Departamento de Especialidades Médico-Quirúrgicas

Programa de Doctorado en Biomedicina

Impact of minimally invasive approach surgery in hepatocellular carcinoma

REVISIÓN SISTEMÁTICA Y META-ANÁLISIS DE RESULTADOS A LARGO Y CORTO PLAZO PARA LAS RESECCIONES HEPÁTICAS LAPAROSCÓPICAS Y ABIERTAS EN EL HEPATOCARCINOMA

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TITULO: *Impact of minimally invasive approach surgery in hepatocellular carcinoma*

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CERTIFICAN:

Que la Tesis Doctoral titulada "**IMPACT OF MINIMALLY INVASIVE APPROACH SURGERY IN HEPATOCELLULAR CARCINOMA/REVISIÓN SISTEMÁTICA Y META-ANÁLISIS DE RESULTADOS A LARGO Y CORTO PLAZO PARA LAS RESECCIONES HEPÁTICAS LAPAROSCÓPICAS Y ABIERTAS EN EL HEPATOCARCINOMA**" ha sido realizada por **Dª. IRENE GÓMEZ LUQUE** bajo nuestra supervisión y dirección.

Para que así conste a todos los efectos, se expide el presente certificado en Córdoba, a seis de Marzo del dos mil veinte.

Dr. D. Javier Briceño Delgado

Dr. D. Rubén Ciria Bru

TÍTULO DE LA TESIS:

Impact of minimally invasive approach surgery in hepatocellular carcinoma
Revisión Sistemática y Meta-análisis de resultados a largo y corto plazo para las resecciones hepáticas laparoscópicas y abiertas en el Hepatocarcinoma.

DOCTORANDO/A: Irene Gómez Luque

INFORME RAZONADO DEL/DE LOS DIRECTOR/ES DE LA TESIS

(se hará mención a la evolución y desarrollo de la tesis, así como a trabajos y publicaciones derivados de la misma).

Durante el desarrollo de la presente Tesis Doctoral, la Doctoranda Irene Gómez Luque ha superado los objetivos científicos y formativos planteados al comienzo de la misma. Al inicio de este trabajo, la Doctoranda realizó una estancia como rotación externa de su especialidad durante un total de 6 meses (2013, 2014 y 2016) en la Unidad de Trasplante Hepático del Hospital King's College de Londres (Reino Unido), bajo la supervisión del Prof. Nigel D. Heaton.

Durante ese período amplío sus conocimientos en el campo de cirugía de Trasplante Hepático y Hepatobiliar. Tras ello formó parte del equipo de Investigación para la elaboración de las primeras Guías Clínicas en Cirugía Hepática Laparoscópica. Dichas guías clínicas fueron realizadas en Southampton, Febrero de 2017,

A raíz del trabajo llevado a cabo en la elaboración de las Guias Clinicas Europeas en Cirugía Hepática Laparoscópica han sido publicados tres artículos científicos en revistas de alto impacto del área de Cirugía Hepatobiliar y Trasplante Hepático. Uno de los cuales fue publicado en la revista Annals of Surgery con un factor de impacto mayor de 9, con una alta difusión siendo una de las bases más establecidas en la Cirugía Hepática Laparoscópica actual.

Por todo ello, se autoriza la presentación de la tesis doctoral.

Córdoba, 6 de Marzo a de 2020

Firma de los directores

Dr. D. Javier Briceño Delgado

Dr. D. Rubén Ciria Bru

SUMMARY OF Ms. Irene Gómez Luque's DOCTORAL THESIS

1. Introduction/Aims of the Thesis

Liver cancer is the fifth most common and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers and constitutes a major global health problem.

According to the World Health Organization (WHO) the incidence rate of HCC has increased in the last three decades and will maintain this trend in 2030. In accordance with the last published world record, 854.000 new cases and 810.000 deaths are diagnosed every year, representing 7% of all cancer's deaths.

The prognosis of the response to treatment is different depending on the type of HCC and its status at the time of diagnosis. For this reason, HCC classification and choice of the most suitable treatment is relevant for a successful response. Surgical approach is the first treatment option in patients with very early-stage and preserved liver function with a 5-years OS rate around 60-80%.

Under the EASL guidelines surgical resection is recommended as the treatment of choice in patients with HCC arising on a non-cirrhotic liver. Indications for resection of HCC in cirrhosis should be based on a multi-parametric composite assessment of liver function, portal hypertension, extent of hepatectomy, expected volume of the future liver remnant, performance status and patients' comorbidities. In patients with chronic liver disease or cirrhosis, the choice of surgical resection should be more debated and, in certain cases, discarded.

Liver Transplant (LT) is recommended as the first-line option for HCC within Milan criteria but unsuitable for resection. Laparoscopic liver approach is now a standard of practice for several procedures and has overpassed the tip point from pioneers to being currently widely adopted by several groups. Because of cirrhotic-associated complexity, laparoscopic liver resection for HCC may be more complex due to different factors: liver failure, coagulopathy, collateral circulation, and parenchymal stifness.

The current situation is a trend towards the expansion of laparoscopic surgery in both simple resection and complex hepatectomies. The early diffusion of this approach made the current Guidelines Meeting in Laparoscopic Liver Surgery another landmark in the field.

2. Contents of the research

The alternative hypothesis proposed for our study was if laparoscopic hepatic surgery offers advantages compared to open surgery in the management of Hepatocellular carcinoma.

The aim of this study was to perform a systematic review and meta-analysis comparing the short- and long-term outcomes of laparoscopic and open liver resections for hepatocellular carcinoma. To evaluate if considering severe morbidity, including liver-specific posthepatectomy liver failure and 90-days mortality, laparoscopic approach offers benefits against the open. To evaluate if laparoscopic approach has an impact on long-term outcomes considering overall survival and disease-free survival. To demonstrate whether laparoscopic approach for the treatment of hepatocellular carcinoma may be considered as the first option and in which cases it could be considered as standard of practice.

To identify all the comparative manuscripts reporting on laparoscopic and open liver resection for HCC, all published English-language studies with more than 10 cases were screened. In addition to the primary meta-analysis, four specific subgroup analyses were performed on patients with Child–Pugh A cirrhosis, resections for solitary tumors, and those undergoing minor and major resections.

The manuscripts included in the meta-analysis are subjected to a double-check quality analysis. That assessment was performed first under the Scottish Intercollegiate Guidelines Network (SIGN) methodology criteria and then in accordance with the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort and case-control studies (Ottawa Hospital Research Institute). This double assessment of each manuscript included is performed to reduce the risk of biases and thus enhance the quality of their results.

Once the first step is completed, the evidence level on the topic is produced based on the quality of the available literature assessed at the previous step. The next step, once the evidence tables of each manuscript have been made, is to produce recommendations according to the evidence found in each one of them for the elaboration of guidelines of liver laparoscopic surgery.

From the initial 361 manuscripts, 28 were included in the meta-analysis. Five of these 28 manuscripts were specific to patients with Child–Pugh A cirrhosis (321 cases), 11 focused on solitary tumors (1003 cases), 16 focused on minor resections (1286 cases), and 3 focused on major resections (164 cases). Three manuscripts compared 1079 cases but could not be assigned to any of the above subanalyses. In general terms, short-term outcomes were favorable when using a laparoscopic approach, especially in minor resections. The only advantage seen with an open approach was reduced operative time during major liver resections. No differences in long-term outcomes were observed between the approaches.

3. Conclusions

- Our exhaustive literature review, and assessment of current evidence by SIGN methodology has been the basis for the development of the European Guidelines Meeting on Laparoscopic Liver Surgery and for the eachievement of consistent, reliable and evidence-based statements in the application of minimally invasive approaches for the treatment of hepatocellular carcinoma.
- According to the results of our updated meta-analysis, a minimally invasive approach might be more beneficial compared to an open approach as it may offer a lower rate of complications, blood loss, transfusion rate and postoperative hospital stay for patients with Child-Pugh A cirrhosis, solitary tumors and those undergoing minor resections.
- Considering severe morbidity including liver-specific posthepatectomy liver failure and 90-days mortality, laparoscopic approach was not different compared to open approach.
- Laparoscopic approach does not have an impact on short-, mid- and long-term outcomes considering overall survival. A trend towards better disease-free survival when laparoscopic approach is used was observed but no robust conclusions may be obtained. Its impact on re-do hepatectomies or on feasibility of rescue or salvage transplantation procedures remains unresolved.
- Considering the optimal results obtained from laparoscopic approach, its use for the treatment of hepatocellular carcinoma should be considered as first option and standard of practice in selected patients from high-volume centers in which a multimodal strategy can be offered to these complex patients.

4. References

1. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018 Jul;69(1):182–236.
2. Mak L-Y, Cruz-Ramón V, Chinchilla-López P, Torres HA, LoConte NK, Rice JP, et al. Global Epidemiology, Prevention, and Management of Hepatocellular Carcinoma. Am Soc Clin Oncol Educ Book. 2018 May 23;(38):262–79.
3. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, Ahmed M, Alam N,

Alemayohu MA, et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. JAMA Oncol. 2017 Dec 1;3(12):1683–91.
4. Global Cancer Observatory. online. 2019 Jul 14;:1–2.
5. Addissie BD, Roberts LR. Classification and staging of hepatocellular carcinoma: an aid to clinical decision-making. Clin Liver Dis. 2015 May;19(2):277–94.
6. Kaneko H, Takagi S, Otsuka Y, Tsuchiya M, Tamura A, Katagiri T, et al. Laparoscopic liver resection of hepatocellular carcinoma. AJS. 2005 Feb;189(2):190–4.
7. Ciria R, Cherqui D, Geller DA, Briceño J, Wakabayashi G. Comparative Short-term Benefits of Laparoscopic Liver Resection: 9000 Cases and Climbing. Annals of Surgery. 2016 Apr;263(4):761–77.
8. Fretland ÅA, Dagenborg VJ, Bjørnelv GMW, Kazaryan AM, Kristiansen R, Fagerland MW, et al. Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. Annals of Surgery. 2018 Feb;267(2):199–207.
9. Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. 2009. pp. 825–30.
10. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han H-S, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. 2015. pp. 619–29.
11. Abu Hilal M, Aldrighetti L, Dagher I, Edwin B, Troisi RI, Alikhanov R, et al. The Southampton Consensus Guidelines for Laparoscopic Liver Surgery: From Indication to Implementation. Annals of Surgery. 2018 Jul;268(1):11–8.
12. Komatsu S, Brustia R, Goumard C, Perdigao F, Soubrane O, Scatton O. Laparoscopic versus open major hepatectomy for hepatocellular carcinoma: a matched pair analysis. Surgical Endoscopy. 7 ed. Springer US; 2016 May;30(5):1965–74.
13. Zhang Y, Huang J, Chen X-M, Sun D-L. A Comparison of Laparoscopic Versus Open Left Hemihepatectomy for Hepatocellular Carcinoma. Surg Laparosc Endosc Percutan Tech. 2016 Apr;26(2):146–9.
14. Lee JJ, Conneely JB, Smoot RL, Gallinger S, Greig PD, Moulton C-A, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma at a North-American Centre: a 2-to-1 matched pair analysis. HPB. 2015 Apr;17(4):304–10.
15. Morise Z, Ciria R, Cherqui D, Chen K-H, Belli G, Wakabayashi G. Can we expand the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. J Hepatobiliary Pancreat Sci. 2015 May;22(5):342–52.

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Aún recuerdo cuando empecé como residente en el Hospital Reina Sofia, con miedos, ilusión y emoción, siendo una carrera de fondo en la que la resistencia y el esfuerzo es la base.
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El éxito en la vida no se mide por lo que logras, sino por los obstáculos que superas.

"(...) Y por robar el secreto del fuego a los Dioses del Olimpo y entregárselo a los hombres, Prometeo fue encadenado en el monte Caúcaso y condenado a que un águila devorase su hígado. El hígado se regeneraba cada día, proporcionando alimento al águila y eterna tortura a Prometeo (...)"

Mito de Prometeo

("Prometeo encadenado", atribuido a Esquilo)

A mi familia...

Y a la que está por venir

ABBREVIATIONS

A

AASLD: American Association for the Study of Liver Diseases
AFP: alpha-fetoprotein
AL: Anterolateral
ALD: Alcoholic Liver Disease
AR: anatomical resection
ASA: American Society of Anesthesiologists

B

BCLC: Barcelona Clinic Liver Cancer staging

C

CI: confidence intervals
CLIP: Cancer of the liver Italian program
CPG: Clinical Practice Guidelines

D

DCDD: Donation after circulatory determination of death

E

ECOG: Eastern Cooperative Oncology Group
EGMLLS: European Guidelines Meeting for Laparoscopic Liver Surgery
ELITA: European Liver and Intestine Transplant Association

H

HCC: Hepatocellular carcinoma
HBV: Hepatitis B Virus
HCV: Hepatitis C Virus
HKLC: Hong-kong Liver Cancer stanging

I

IC: intermittent clamping
ILTS: International Liver Transplantation Society
IwS: Iwate Score

J

JIS: Japanese Integrated staging

L

LLS: Laparoscopic liver surgery
LLR: Laparoscopic liver resections
LMH: Liver Major hepatectomy
LT: Liver transplant

M

MC: Milan Criteria
MELD: Model of End-Stage Liver Disease

N

NAR: Non-anatomical resection
NASH: Non-alcoholic steatohepatitis
NAFLD: Non-alcoholic fatty liver disease
NOS: Newcastle-Ottawa Quality Assessment Scale

O

OLR: Open Liver resection

P

PHLF: post-hepatectomy liver failure
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PS: Postero-superior
PSM: Propensity score matching

R

RFA: Radiofrequency

S

SIGN: Scottish Intercollegiate Guidelines Network
SoF: Summary of findings

T

TACE: Transarterial chemoembolization
TNM: tumor-node-metastasis staging

U

UCSF: University of California at San Francisco

W

WHO: World Health Organization
WMD: weighted mean difference

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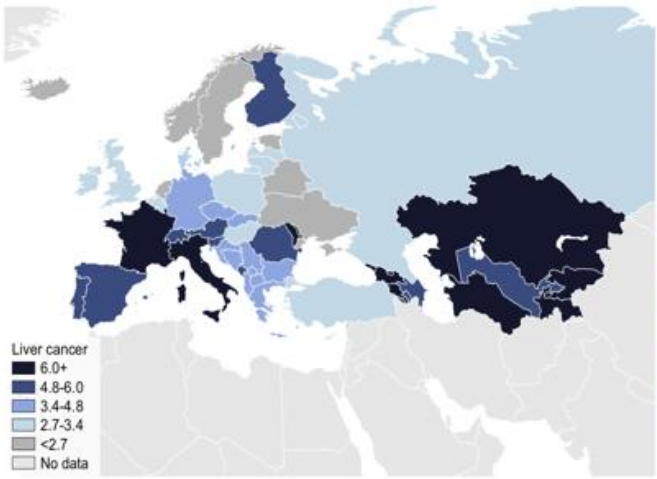
1. INTRODUCTION

1.1. Overview of Hepatocellular Carcinoma

1.1.1. Historical Introduction

Liver cancer is the fifth most common and the second most frequent cause of cancer-related death globally. Hepatocellular carcinoma (HCC) represents about 90% of primary liver cancers and constitutes a major global health problem (1). According to the World Health Organization (WHO) the incidence rate of HCC has increased in the last three decades and will maintain this trend in 2030 (2). In accordance with the last published world record, 854.000 new cases and 810.000 deaths are diagnosed every year, representing 7% of all cancer's deaths (3).

HCC incidence has increased according to the ageing of the population. The decade of the 70's is the most common age for diagnosis. However, the distribution of age at diagnosis varies according to demographic characteristics of the population. In countries such as China or Africa, the age of diagnosis is lower. The incidence of HCC is more frequent in male than in female with a ratio of 2-2.5:1 (4). Geographical distribution of HCC does not show a clear pattern. A high incidence can be observed in East of Asia and South of Africa with another hot zone in the South of Europe. At the moment, an HCC's pattern of distribution has not been described yet despite the increase of its incidence in recent years (Figure 1).



Population numbers

Italy	10,733	The Netherlands	475
Germany	9,202	Croatia	466
France (metropolitan)	8,332	Republic of Moldova	448
Russian Federation	6,812	Slovakia	398
Spain	5,522	Belarus	327
United Kingdom	4,186	Bosnia Herzegovina	314
Romania	2,214	Denmark	311
Poland	1,998	Ireland	239
Ukraine	1,567	Slovenia	216
Greece	1,054	Norway	190
Portugal	1,004	Lithuania	175
Austria	955	Albania	171
Czech Republic	919	Latvia	154
Switzerland	811	FYR Macedonia	135
Serbia	799	Luxembourg	68
Belgium	645	Estonia	64
Bulgaria	640	Cyprus	56
Hungary	630	Montenegro	51
Finland	620	Malta	19
Sweden	490	Iceland	10

Figure 1. Incidence rates of primary liver cancer according to geographical distribution in Europe. Total numbers per country and age-adjusted incidence rates per 100.000 of liver cancer in Europe in 2012. Source: GLOBOCAN 2012. IARC

Several risk factors have been reported in the physiopathology of the HCC. Chronic hepatitis B virus infection (HBV), Chronic hepatitis C virus infection (HCV), Non-alcoholic fatty liver disease (NAFLD), Non-alcoholic steatohepatitis (NASH), alcoholic liver disease (ALD), hereditary hemochromatosis and other etiologies have been associated with the development of HCC.

1.1.2. Hepatocellular Carcinoma Classification

Hepatocellular carcinoma is an heterogeneous tumor with different onsets. It can be diagnosed as a single nodule on a healthy or cirrhotic liver, as a large lesion along more than half of the liver with or

without lymph node involvement or distant metastases or as a multinodular tumor.

The prognosis of the response to treatment is different depending on the type of HCC and its status at the time of diagnosis. For this reason, HCC classification and choice of the most suitable treatment is relevant for a successful response. Liver cirrhosis is an important prognostic factor for the response to treatment as well as for the recurrence rate in the follow-up.

Table 1. Tumor-Node-Metastases Staging

Stage	Tumor	Node	Metastasis
Stage I	T1: solitary tumor without vascular invasión	N0: No regional node metastasis	M0: No distal metastasis
Stage II	T2: Solitary tumor with vascular invasion or multiple tumors <5 cm		
Stage IIIA	T3: Multiple tumors>5 cm or tumor involving major branch of the portal vein		
Stage IIIB	T4: Tumor that invades adjacent organs other tan gallbladder or perforates visceral peritoneum		
Stage IIIC	Any T	N1: Regional lymph node metastasis	
Stage IV	Any T	Any N	M1: distant metastasis

AJCC Cancer Staging Manual. 7th ed. New York, Springer; 2010. P. 222

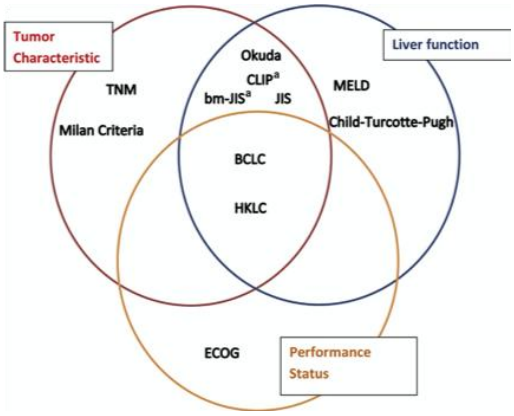


Figure 2. Variables used in various HCC classification and staging methods.

Incorporated serum biomarkers, such as alpha-fetoprotein. Benyam D et al. Classification and Staging of Hepatocellular carcinoma. An Aid to clinical decision-making. Clin Liver Dis 19 (2015) 277-294.

Different classifications and staging systems (Figure 2) have been developed in the last decades.

Several factors have been included. Some of them are common shared among them, such as size, numbers of nodules, location, liver dysfunction and performance status. Some others are not common and are intrinsic to each system (5).

TNM Classification

This system is based on the standardized solid tumor classification system that was reported in 1968 by the french surgeon Pierre Denoix. The TNM classification (Table 1) consists of three variables, tumor size, the presence and extension of lymphatic involvement and the presence of distant metastases.

Its limitation is that it does not take into account or evaluate the existing liver function. However, it has been proven that the TNM classification has greater prognostic capabilities than the Okuda classification or CLIP score (6).

Okuda Classification

The Okuda classification (Table 2) was published in 1985 (7). This staging system was the first score in which the liver function is included based on the presence of bilirubin, ascites and albumin.

Tumor size is another of the items included (greater or lesser than 50% of the liver). The way in which it classifies the tumoral size could be the main drawback of this classification since the tumor

size is currently an important prognostic factor for the choice of treatment.

Table 2. Okuda Classification

	0 point	1 point
Tumor size	<50% of liver	>50% of liver
Ascites	No	Yes
Albumin	>3 g/dL	<3 g/dL
Total bilirubin	<3 mg/dL	>3 mg/dL
Stage I (0 points); Stage II (1-2 points); Stage III (3-4 points)		

Cancer of the Liver Italian Program

This staging system is based on tumor morphology (nodular or multinodular), presence of portal thrombosis and liver function. The CLIP (Table 3) system was reported in 1998 (8). This classification has shown to be a good indicator of long-term results after therapies with curative intention.

Table 3. Cancer of the liver Italian Program (CLIP)

	0 Points	1 Points	2 Points
Child-Turcotte-Pugh class	A	B	C
Tumor morphology	Single tumor and <50% of liver	Multiple tumors and <50% of liver	>50% of liver
Alpha-fetoprotein	<400 ng/mL	>400 ng/mL	
Portal vein thrombosis	No	Yes	
Early stage (0 points); Intermediate stage (1-3 points); Advanced stage (4-6 points)			

Table 4. Japanese Integrated Staging Score

	0 Point	1 Point	2 Points	3 Points
TNM	I	II	III	IV
Child-Turcotte-Pugh class	A	B	C	
JIS Score: Sum of points				

Japan Integrated Staging

The Japan Integrated Staging (JIS) is a score based on the combination of the TNM system and the liver function evaluated by the Child-Pugh classification (Table 4). These variables are grouped into intervals with a score of 0 to 5 points. The JIS system was updated in 2008 (9) adding serological markers to the variables evaluated.

Barcelona Clinic Liver Cancer Staging (BCLC)

In 1999, the Barcelona Clinic Liver Cancer Staging (BCLC) classification was described (10) and proposed as a classification and staging system. BCLC classification is based on tumor's variables (size and extension, macrovascular invasion and extrahepatic dissemination), liver function (Child-Pugh classification), performance status of the patient and the presence of any constitutional symptoms related with the tumor.

The BCLC system is considered one of the best and more used scores for HCC classification. For this reason, BCLC has been chosen by the European Association for the Study of the Liver Clinical Practice Guidelines and American Association for the Study of Liver Disease as the main pathway to the clinical management of HCC. It has been extensively validated (11).

This system links the tumor stage with the treatment strategy in a dynamic way, which is its greatest advantage. This characteristic allows the incorporation of novel advances in understanding the prognosis and the management of HCC (1).

A prognostic classification that includes all the involved variables is difficult to obtain. The BCLC classification (Figure 3) allows for a clear definition of the prognosis for each patient as well as for the treatment to be applied in a more objective way.

According to the progresses in several fields as oncology, radiotherapy, interventional radiology and especially laparoscopic liver surgery, certain limitations have been observed in the BCLC classification. Within the BCLC-B and BCLC-C stage, a large number of patients with very heterogeneous characteristics are grouped. These patients should be evaluated in a more individual way because some patients could currently benefit from more aggressive therapies with curative intention-to-treat, offering lower rate of complications.

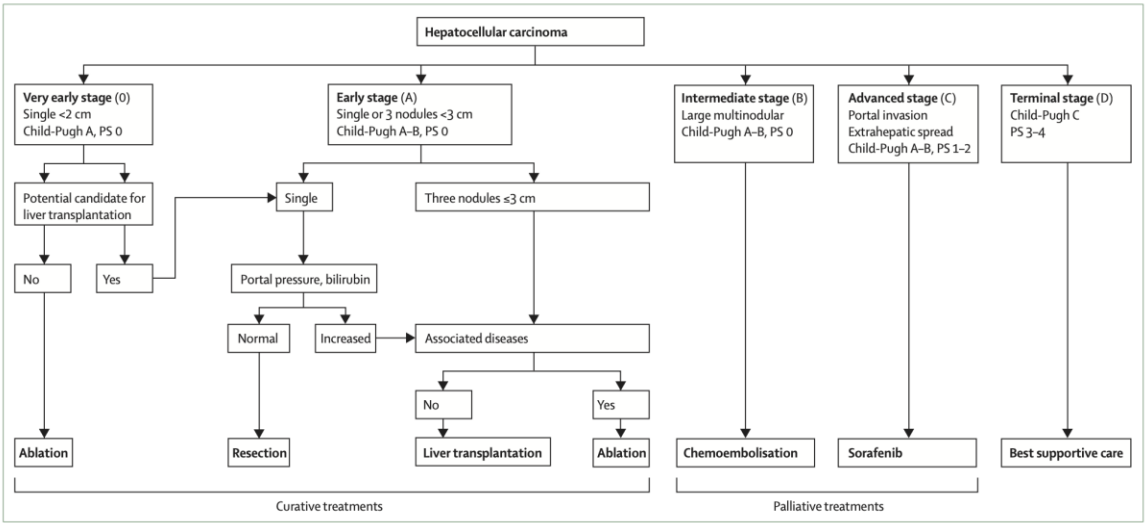


Figure 3. The BCLC system establishes a prognosis in accordance with the five stages that are linked to first-line treatment recommendation. If the recommended option is not feasible because of an individual patient's condition, the treatment approach for the next evolutionary disease stage should be considered.

(Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012 Mar 31;379(9822):1245–55)

Thanks to high resolution radiological imaging, HCC can be diagnosed in earlier stages. This improvement in diagnosis has turned in the definition of a new stage in the HCC classification (Stage 0) (12). Therefor, different modifications have been established with new chemotherapeutic schemes being added. One of the latest updates is the incorporation of radiofrequency for the treatment of HCC< 2 cm (13).

Hong Kong Liver Cancer Prognostic Staging Scheme

Hong Kong Liver Cancer Prognostic Staging Scheme (HKLC) is the most recent published score (14). HKLC (Figure 4) is similar to the BCLC classification. However, this score shows more aggressive attitudes towards patients with tumors in advanced stages, which leads to a better prognosis than other scores. HKLC is based on a chronic liver disease population with HBV as the leading etiology and may not be generalizable to regions with a high prevalence of hepatitis C virus or alcoholic liver disease-induced HCCs (5).

1.2. Therapeutic strategies of Hepatocellular Carcinoma

There is a wide range of therapeutic possibilities in the treatment of HCC. Techniques with curative intention are ablative therapies, surgical resection or liver transplantation (LT). Systemic chemotherapy treatment and support for and adequate treatment with palliative measures are strategies applied to advanced stages of the disease.

The different scores, referred in the previous section, act as a tool to identify the most suitable treatment for each patient with the highest survival rate. Due to the heterogeneity in the HCC's presentation and the specificity of the current treatments, the decision of each treatment must be taken by a specialized committee including hepatologists, interventional radiologists, oncologists, liver surgeons and intensivists.

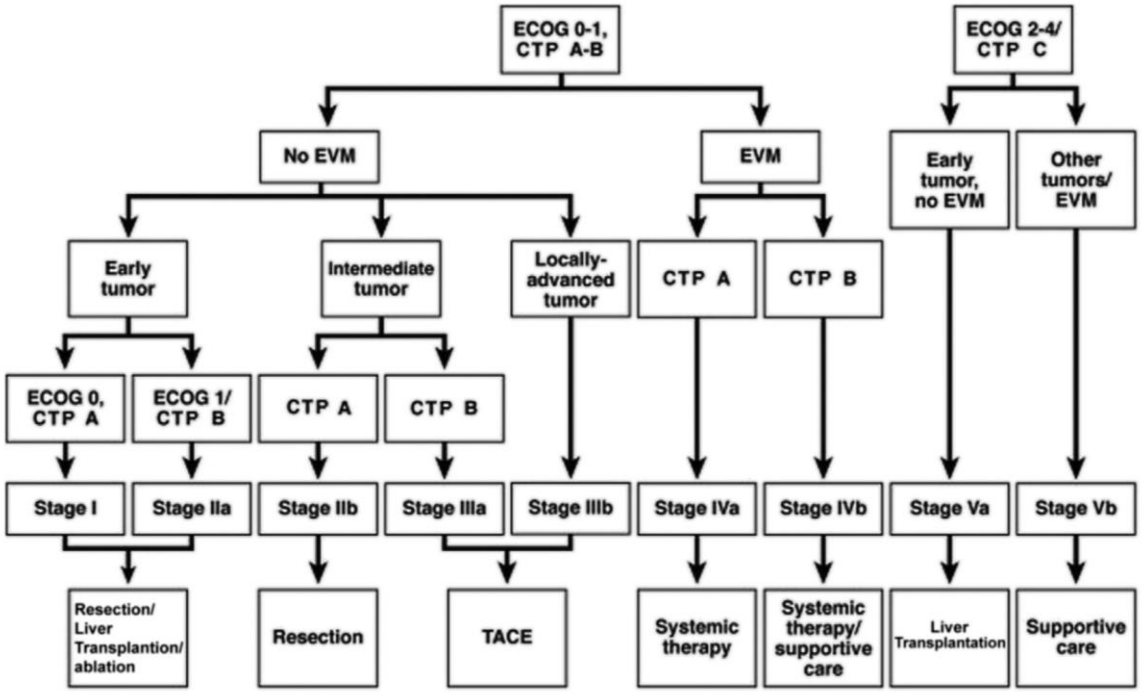


Figure 4. Hong Kong Liver Cancer Stanging (5,14)

1.2.1. Ablative Therapies

Radiofrequency (RFA) and chemoembolization (TACE) might be considered the most used ablative techniques.

RFA can be defined as the necrosis or destruction of tumor's tissue using a thermal mechanism generated by radiofrequency (15). The damage caused by RFA is due to the heat friction produced by the ionic agitation of the particles close to the tissue as a consequence of the application of an alternate current.

On the other hand, TACE is performed by the injection of a combination of chemotherapeutic agents with polyvinyl alcohol particles with the objective of embolizing the branch of the hepatic artery that perfuses the tumor and achieving a sustained release of the chemotherapeutic agent (generally doxorubicin, cisplatin and/or mitomycin C) to induce ischemia or necrosis of the tumor (5).

RFA is a safe and effective treatment of small HCC in cirrhotics awaiting OLT as a bridge treatment or as a downstaging technique, although tumor size >3 cm and time from treatment >1 year predict a high risk of tumor persistence in the targeted nodule (16).

The survival rate provided by RFA is 95.5%, 59.7% and 32.3% at 1-, 5- and 10 years respectively (17). Although it could be considered a more innocuous treatment than surgical resection or liver

transplantation, RFA is not free of complications. An overall complication rate of 4.1% and a mortality rate of 0.15% have been reported in the literature (18). In addition, a series of absolute and relative contraindications have been reported since not all HCCs are subsidiary of ablative treatment (Table 5).

Table 5. Contraindications to thermal ablative treatments

Absolute contraindications
Extrahepatic disease
Altered mental status
Active infection
Tumor abutting a major hepatic duct
Liver decompensations
Relative contraindications
Lesions>5 cm
More than 4 lesions
Severe pulmonary o cardiac disease
Refractory coagulopathy

Courtesy of World J Gastrointest Pharmacol Ther 2016 November. Local ablative treatments for hepatocellular carcinoma: An updated review.

Surgical resection might be considered the treatment of choice for HCCs. Hepatectomy and percutaneous RFA are the two best treatment options for small HCC. Current studies have been designed to compare the efficacy of RFA with surgery in early stages of HCC. Four randomized studies have been published comparing the results of both techniques, in those studies, the superiority of the surgical approach over the RFA in terms of survival and recurrence was found (19) (20) (21) (22).

In these studies, no differences in survival rates for both methods have been found for tumors < 2cm. However, relevant selection biases were observed in those studies. Patients in the RFA group have a poorer liver function and are older, leading to a worse prognosis (23) (24). By performing subgroup analyses, it was observed that for very early-stage HCC and in the presence of two or three nodules <3cm, RFA is more cost-effective and provided similar survival and recurrence rates than surgical resection (25).

According to the BCLC classification, transarterial chemoembolization (TACE) is the first line of treatment for intermediate stages, which includes asymptomatic patients with unresectable or multinodular lesions, without vascular invasion or extrahepatic disease who have a preserved liver function (26).

In the latest published reviews, the BCLC system accepts TACE as a treatment for patients with early-stage HCC in which the other therapeutic strategies can not be used or have failed. There are two options, conventional TACE-Lipidol and TACE with drug-eluting beads (DEB-TACE). A current meta-analysis has shown that there are no differences between both techniques in terms of tumor response and survival rate (27).

Therefore, TACE could be considered an intention-to-treat technique that provides an increase in survival rate in intermediate BCLC stage patients. Besides, according to the current EASL guidelines, this technique is recommended as neoadjuvant therapy prior to LT, as a bridge treatment on the waiting list or as a downstaging technique to satisfy LT criteria.

Actually, several studies have been carried out to evaluate the combined use of both ablative therapies (RFA and TACE).

In a recent meta-analysis in which 8 RCTs were analyzed including 598 patients, the combination of both techniques offered a significantly higher 3 year OS rate [odds ratio (OR): 2.65, 95% CI: 1.81-3.86, $P < 0.001$] and 3-year RFS rate (OR: 3.00, 95% CI: 1.75-5.13, $P < 0.001$) than the treatment with RFA alone, with equivalent complications rate (28).

In the subgroup analysis, the survival rate was significantly higher in patients with intermediate-stage and larger size HCC who were treated with this strategy than with other therapies but did not improve the survival rate in patients with smaller HCC.

Therefore, these results concluded that the combination of RFA and TACE were beneficial to in terms of survival and recurrence rate in those HCC

cases classified as intermediate-stage with larger size.

1.2.2. Surgical Approach

Surgical approach is the first treatment option in patients with very early-stage and preserved liver function (29) with a 5-years OS rate around 60-80%. Under the EASL guidelines (1) surgical resection is recommended as the treatment of choice in patients with HCC arising on a non-cirrhotic liver.

Indications for resection of HCC in cirrhosis should be based on a multi-parametric composite assessment of liver function, portal hypertension, extent of hepatectomy, expected volume of the future liver remnant, performance status and patients' comorbidities. In patients with chronic liver disease or cirrhosis, the choice of surgical resection should be more debated and, in certain cases, discarded.

The ideal patient diagnosed with HCC on a cirrhotic liver candidate to surgical resection was reported on the 2012 EASL guidelines and should meet several criteria: solitary tumor with preserved liver function, systemic-portal gradient <10 mm Hg or platelet count >100.000/mL. The fulfilment of all these requirements is very complex and unusual in clinical practice. These patients are much more complex, with greater comorbidities and a higher rate of postoperative complications. The choice of surgical treatment is based on a complex decision, that depends on the characteristics of each patient.

Different advances in surgical techniques, such as the development of laparoscopic liver surgery and perioperative management have improved surgical outcomes in cirrhotic patients. These changes have led to an expansion in the inclusion criteria for the choice of surgical resection as the first therapeutic option. In this way, a greater proportion of patients might benefit from this treatment.

EASL has established as a prognostic or risk factors for the surgical indication in cirrhotic patients the presence of portal hypertension, the extension of hepatectomy and liver function (Figure 5).

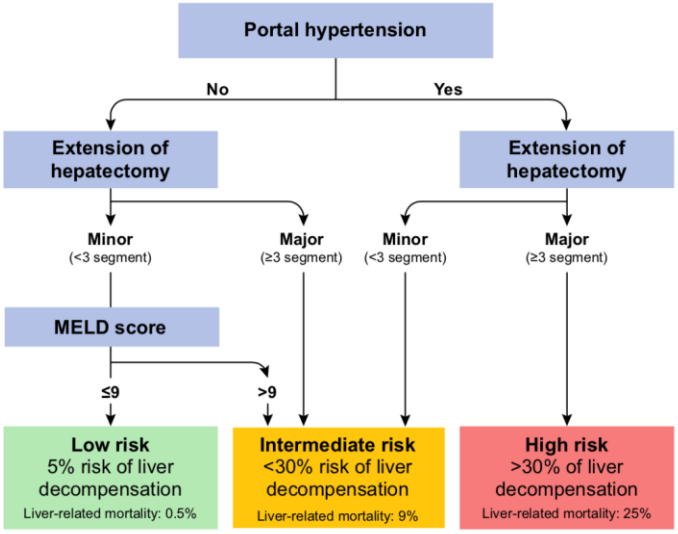


Figure 5. Multiparametric assessment of the risk of liver decompensation after LR for HCC in cirrhosis.

EASL Guidelines (2018)

Once the previous criteria have been met, the indication of the surgical approach for an HCC has to take into account other important factors such as size and location of the tumor, as well as the number of tumors (nodular or multifocal tumour). For HCCs ≤2 cm located in the peripheral parenchyma, liver resection by minimal-invasive approach is the treatment of choice. But when the HCCs are located deeply or centrally, RFA has to be considered because it offers better cost-effective results with the same survival rates (1).

The size of the tumor is a very important prognosis factor. Studies have confirmed that post-resection outcome decreases as the tumor size increases. For this reason, the threshold of 5 cm is considered as the limit for intermediate-stage HCC in Hong Kong Liver cancer Prognostic Staging. Certain studies propose the extension of surgical approach for patients in BCLC stage B and C, as long as the extension of the resection and the liver function are taken into account (30).

Others important published factors that have been evaluated and must be fulfilled to obtain a successful resection are: MELD≤9, Child-Pugh A and PS<2 (31). In multifocal HCCs, the choice of treatment is still under debate. The published studies may be biased due to their retrospective nature and meta-analyses based on non-randomized studies with a low grade of evidence. If patient performance status and co-morbidities allow for surgical resection, and if liver function and remnant liver volume-preserving principles are met, HCCs presenting multiple nodules are not a contraindication per se for surgical approach (1).

1.2.3. Liver Transplant

Liver Transplant (LT) is recommended as the first-line option for HCC within Milan criteria but unsuitable for resection (1).

Milan Criteria (MC) are used in HCC patients who are candidates to LT. The expected five-year survival rates after LT for HCC meeting MC are 65-80%. Mazzaferro published the Milan Criteria in 1996 (32). This study was performed over 48 patients who were candidates for LT. The conclusions were that MC was an accurate predictor of good survival rates after liver transplantation (Table 6)

The Milan Criteria have been used for more than 20 years due to the high survival rate and low recurrence rate in the patients who met its requisites. The MC were included in the BCLC staging system, the American Association for the Study of Liver Diseases (AASLD) and the European Association for the Study of the Liver-European Organisation for Research and Treatment of Cancer (EASL-EORTC) practice guidelines.

Table 6. Milan Criteria

Criteria
— Single tumor ≤ 5 cm or — 2-3 tumors not exceeding 3 cm, and — No vascular invasion and/or extrahepatic spread
Milan Criteria (Mazzaferro et al. 1996)

Mazzaferro suggests that the tumour size and number used as criteria for transplantation should be defined at a regional level depending on the dynamics of the waiting list, the proportion of patients with and without HCC on the waiting list, the harm to the patients remaining on the waiting list and the donor availability.

However, with the increase in the donors' pool and the advances in diagnosis and treatment, some restrictions and limitations have been observed in MC. Several groups have proposed different expanded criteria with acceptable results.

Yao et al. proposed that patients with HCC meeting the following criteria: solitary tumor ≤ 6.5 cm, or ≤ 3 nodules with the largest lesion ≤ 4.5 cm and total tumor diameter ≤ 8 cm, had survival rates of 90% and 75.2%, at 1 and 5 years, respectively, after LT versus 50% at 1-year survival for patients with tumors exceeding these limits ($p = 0.0005$) (33).

In 2002, Roayaie et al. created a multimodal protocol where patients free of extrahepatic disease and unresectable HCC measuring 5 cm or larger were included. Patients underwent pretransplant arterial chemoembolization and systemic

chemotherapy for a total of six cycles. A tumor size larger than 7 cm and the presence of vascular invasion significantly correlated with HCC recurrence (55% vs 34%).

Authors concluded that patients with HCC measuring 5 cm or larger may achieve adequate long-term survival rates after LT in the context of adjuvant therapy (34). Subsequently, Duffy et al. published a study comparing 467 patients, 126 of them fulfilled the Milan criteria, 208 fulfilled the UCSF criteria (single tumor <6.5 cm, maximum of 3 total tumors with none >4.5 cm, and cumulative tumor size <8 cm) and 133 exceeded the UCSF criteria.

Overall survival and recurrence rates were compared for each group. Overall survival rates for the entire group at 1, 3, and 5 years after transplantation was 82%, 65%, and 52% respectively.

Authors reported that post-transplant survival rates for patients with tumors within UCSF criteria (either by pretransplant imaging or pathologic examination) was similar to the survival rate of tumors within the Milan criteria. They found poorer survival rates for patients with tumors beyond the UCSF criteria, with 3 and 5-year survival rates below 50% (35). Even the BCLC group published an expanded criteria that include one tumor <7 cm, 3 tumors <5 cm, 5 tumors <3 cm, or down-staging to conventional Milan criteria with pretransplant adjuvant therapies (1). With this approach, they showed a better survival rate compared to support palliative treatment alone (50% vs 20%) at 5-years post-LT.

At present, European Liver and Intestine Transplant Association (ELITA) and International Liver Transplantation Society (ILTS) have developed an interesting project, which offers a prognosis calculator to obtain the survival rate of each patient candidate for a transplant which is related to HCC. The Metroticket is based on pre-transplant tumor determinants at radiology staging (e.g. maximum size of the vital HCC and number of vital HCC nodules) combined with the serum alpha-fetoprotein (AFP) level (*www.hcc-olt-metroticket.org*).

Current literature seems to support that the modest expansions of LT criteria for HCC beyond MC offer comparable results to the ones of the Milan criteria.

The indication for LT in HCC is a complex decision. Currently, many factors influence it. There is a general concern about how the expansion criteria for LT related HCC could have an impact on the waiting list.

The Michigan group studied such possible influence by performing a Markov theoretical model comparing the survival benefit of transplanting a patient with HCC beyond the MC and the harm caused to the other patients on the waiting list. They showed that the expansion criteria could induce an increase in the risk of death on the waiting list (36).

These conclusions should be taken with caution. The waiting list is influenced by a multitude of factors, including demographic factors. In the last few years, there has been a change in the pattern of patients on the waiting list. On one hand, the introduction of new antiviral therapies has led to a decrease in LT related HCV, which has a direct impact on the increase of the waiting list. On the other hand, the donor's pool is changing, which could decrease the waiting list.

The use of expanded criteria donors, aged donors, donor after circulatory determination of death (DCDD), living-related donor and the use of perfusion machines may lead to an increase in the number of donors. The decision on whether to expand the HCC transplantation criteria or not should probably be done at a regional level after analysing the impact of all variables previously described (37).

1.3. Development of minimally invasive liver surgery

1.3.1. Historical Evolution

There are several manuscripts in which procedures similar to a laparoscopy began to be performed around 1901 (38). This technique had a widespread

in Europe, where laparoscopy was performed mostly for diagnosis.

In 1991, Reich et al. published the first laparoscopic liver resection for a benign tumor (39). In 1996, Azagra and Kaneko reported the first series of anatomical resections performed by laparoscopic approach (40, 41). However, the evolution of LLS has been slower than other surgical specialities, probably due to the complexity of hepatobiliary surgery.

The first resections consisted of lesions located on the anterior or inferior segments, pedunculated or small size lesions with a benign nature. Due to the parallel advance of the surgical devices (harmonic scalpel for liver transection and others) and the development of the laparoscopic surgeon's learning curve, the evolution of LLS has grown exponentially.

The progression of laparoscopic liver resections in recent years has been exponential and now, complex liver resections, major hepatectomies, sequential procedures and even living donation are performed laparoscopically.

In the development of surgeons' learning curves, liver resections became increasingly complex. In an effort to easily estimate the difficulty of the LLS before surgery, a novel difficulty scoring system was created to define the range of difficulty of liver resection (42). The Iwate Score (IwS) was developed due to the complexity of LLS procedures.

The IwS (Figure 6) is the most universally extended score. This score is based in a range from 0 to 12 points, that defines the complexity of the surgical procedure. The location of the lesion (segments), its size, proximity to vessels, type of resection (segmentectomy, partial resection), liver function and the use of hybrid techniques are the items of IwS. Recently, IwS has been validated in a multicenter study by Tanaka et al. over 2.199 patients from 74 Japanese centres (43).

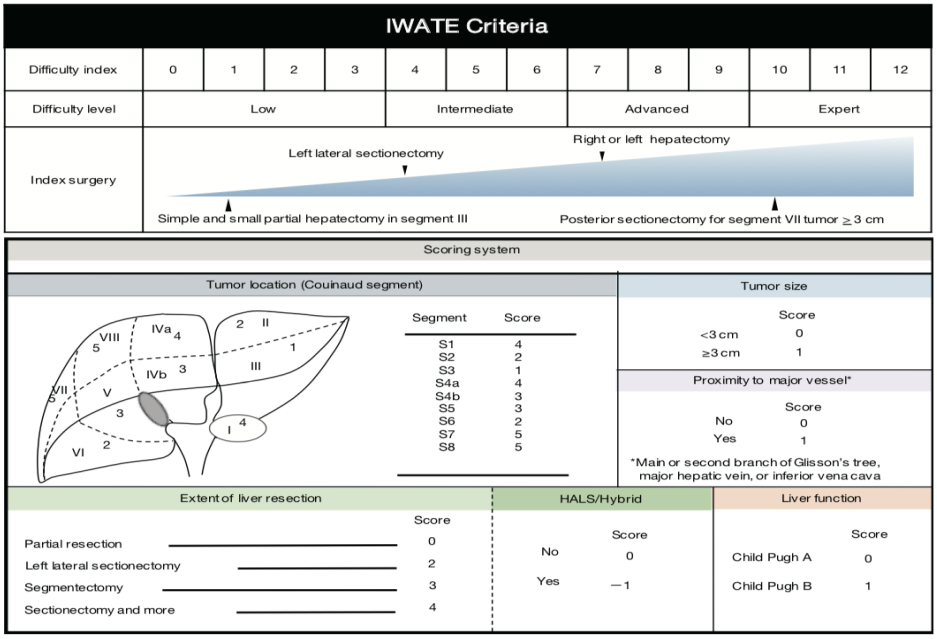


Figure 6. IWATE criteria proposed at the ICCLLR as an up-versioned difficulty scoring system. ICCLLR, International Consensus Conference on Laparoscopic Liver Resection.

In this study, they concluded that the difficulty encountered by surgeons is based mainly on the characteristics of the tumor (localization-anterior/inferior- size and proximity to hilum) and the presence of liver dysfunction. These factors were in correlation with the conversion rate, intraoperative bleeding, operative time and mortality.

IwS could be a valuable tool for assessing the difficulty of LLR and predicting intra- and postoperative complications after LLS. To date, several different scores have been published based on different items in order to achieve a greater predictive value (44) (45). The purpose of these scores is to achieve a possible prediction of the difficulty of the liver resection. These scores may also be useful from an academic point of view and in order to settle an adequate learning curve.

Since the introduction of laparoscopic surgery in 1990, the evolution of this approach has been exponential; from partial resection, left lateral sectionectomy, hemihepatectomy, sectionectomy, segmentectomy, resection of posteriosuperior segments until parenchymal preserving limited and modified anatomical resection.

1.3.2. Current situation

Laparoscopic liver approach is now a standard of practice for several procedures and has overpassed the tip point from pioneers to being currently widely adopted by several groups.

Because of cirrhotic-associated complexity, laparoscopic liver resection for HCC may be more complex due to different factors: liver failure, coagulopathy, collateral circulation, and parenchymal stifness.

A concern on oncological safety may also arise in the setting of laparoscopic liver surgery for malignancies. May it offer any benefit compared to open approach? Is it possible to perform this approach in complex liver resections? Several comparative studies have been published to find the answers to these questions.

In the early 2000s, a large series of laparoscopic cases of HCCs was published (46) (47), reporting the extension of this approach and its use for complex resection on cirrhotic livers. During the last Consensus Conference that was held in Morioka in 2014, a systematic review and meta-analysis of more than 9.000 cases collected from the available literature was carried out (48). The current situation of the laparoscopic approach in liver surgery is reflected in this systematic review and meta-analysis published by Ciria et al (Figure 7).

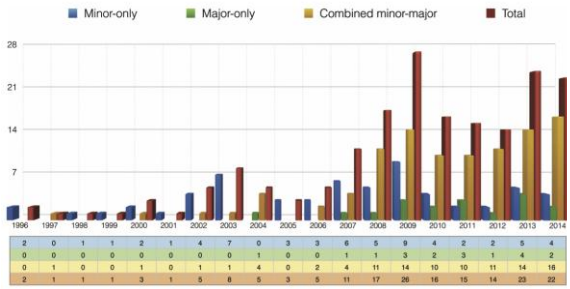


Figure 7. Laparoscopic liver resection reported series. Number of yearly reported manuscripts of laparoscopic liver resections including comparative laparoscopic vs open procedures and case series

(*Courtesy of Ciria et al. Annals of Surgery 2016*)

The main objective of this review was to offer a global perspective of the worldwide status of the laparoscopic approach and secondly, to perform a meta-analysis regarding short-term outcomes of laparoscopic vs open approach. Their findings show that the laparoscopic approach might be considered a feasible alternative to the open approach in minor and major resections without vascular or biliary reconstructions.

This meta-analysis also shows that laparoscopic approach is associated with fewer complications, less blood loss, fewer transfusions, and shorter hospital stay, with equivalent operative time and equivalent resections margins, especially in minor liver resections (Level of Evidence 2+, grade of recommendation B). After Morioka Consensus, nonanatomic wedge and left lateral resection were considered as the standard practice in several centres.

The recent publication of the first randomized trial (The OSLO-COMET Randomized Controlled Trial) comparing laparoscopic vs open approach in colorectal liver metastases (49) can be considered as a true landmark in minimally invasive liver surgery. Two hundred and eighty patients with liver metastases were randomly assigned to laparoscopic (n=133) or open (n=147) resection.

The main objective of this study was to compare postoperative complications in the first 30 days after surgery, the difference in terms of quality of life, blood loss, hospital stay, operative time and differences in oncological terms. The study shows that laparoscopic approach reduced postoperative complications, offered the same oncological safety (equality resection margins) and was more cost effective, with similar costs but higher QALYs than open resection.

Their conclusions are that laparoscopic surgery is a safe approach that presents a lower rate of postoperative complications and does not present any difference in oncological terms. They emphasize that these conclusions should be taken with caution since these results might only be applied in high-volume centres and performed by surgeons with a wide learning curve in LLS.

The current situation is a trend towards the expansion of laparoscopic surgery in both simple resection and complex hepatectomies. The early diffusion of this approach made the current Guidelines Meeting in Laparoscopic Liver Surgery another landmark in the field.

1.3.3. Consensus meetings and European Guidelines

The spread of LLS and the increasing number of series published have made Consensus and Guidelines Meeting a feasible tool in order to make an objective analysis of literature. Two consensus meetings have been held to date. The first one in 2008 and the second in 2014. Recently, in 2017, the first European Guidelines Meeting on Laparoscopic Liver Surgery was held in Southampton.

The objective of these Consensuses was to analyze the evidence published to date with regards to laparoscopic liver surgery.

In the Louisville Conference (50), 45 recognized experts met to define the status of LLS and its future challenges. The sections of this meeting were: indications for surgery, patient selection, surgical techniques, complications, patient safety and surgeon training.

The conclusions of the Louisville consensus settled a basis for the incoming years. First, the indications for laparoscopic liver resections were defined: solitary lesions of 5 cm or less and/or located in anteroinferior segments (2-6).

Based on the experts' opinion, major laparoscopic hepatectomies were considered to be carried out only in specialized centres and by expert surgeons. The role of hand-assisted and hybrid approaches was also defined for complex cases. Regarding living donation, experience with pure laparoscopic approach for pediatric and hybrid for adult was also stated. Nevertheless, both approaches were considered procedures with few evidence and to be performed in the context of a worldwide registry in order to avoid donor complications and/or death.

Concerns on oncological results have increased in parallel. In this consensus, great importance was given to the achievement of safety margins and the detection of hidden lesions. In the published cases, no differences were observed in terms of survival or oncological margins between the two approaches.

The conclusions were that the laparoscopic approach could obtain similar results in oncological terms than the open approach and that the existence of an adequate preoperative image study is of great importance.

In summary, the experts concluded that the laparoscopic approach is safe and effective for the treatments of liver lesions. This approach should be carried out in specialized centres and by expert surgeons. The creation of global societies, meetings and international registries is of great importance

for the establishment of clinical guidelines and universal indications.

The consensus meeting held in Louisville (50) reviewed the feasibility of LLS and settled the first indications and recommendations from very early adopters in this field. Six years later, the second consensus of laparoscopic liver surgery was held in Morioka.

The Morioka Consensus (51) focused on a comparison with open resections and added an extensive literature search using GRADE method, showing the widespread of LLS and its role in the modern era of liver surgery (52).

This consensus was carried out with a more scientific basis, in terms of current literature evidence and analysis. The organizing committee invited 43 respected surgeons, that is, an expert panel with 34 members with demonstrated experience in LLR, plus 9 jury members, to provide evidence and draw recommendations (51). Seventeen questions were posed, the first seven focused on the risks and benefits of this approach and the other ten on its technical aspects.

Due to an exhaustive review of literature, the gathered answers to these questions generated statements and recommendations that were expected to be accepted worldwide and to be used as an uniform guideline in all liver surgical centres.

For minor resections, laparoscopic approach was defined as the standard practice due to the lower complication rate and shorter hospital stay compared to the open approach. Similar results were observed in major resections, although the number of available series was lower.

In regards to technical questions, the caudal approach was presented as a novel concept to optimize hilar dissection and liver parenchymal transection. The lateral approach for the dorsal view was also reported as a feasible technical approach for the resection of lesions located in posterior segments.

In 2017, the last meeting of experts was held in Southampton for the creation of the Clinical Guidelines for Laparoscopic Liver Surgery. The aim of these Guidelines was to provide to both experienced and training surgeons opinions to reduce variations in practice and to facilitate the safe expansion of LLS with the goal of improving patient care (52).

Table 7. Methodology used in the European Guidelines for laparoscopic liver surgery

SIGN methodology	To asses the evidence and develop guideline statements
Delphi method	To establish experts consensus
AGREE II-GRS	To assess the methodological quality and validate the final statements

The methodology for the analysis of the literature was a meticulous process using three validated methods: the SIGN methodology (Scottish Intercollegiate Guidelines Network), the Delphi method and the AGREE II-GRS (Global Rating Scale) instrument (Table 7).

Table 8. Sections of EGMLLS (European Guidelines Meeting for Laparoscopic Liver Surgery)

Section 1: Indications
Topic 1: Colorectal Liver Metastases (CRLM)
Topic 2: Bening and rare non-colorectal Metastases
Topic 3: Hepatocellular Carcinoma (HCC)
Topic 4: Living donor
Section 2: Patients and Complex Diseases
Topic 5: High-risk Patients
Topic 6: Redo Liver Resections
Topic 7: Technically Complex Settings
Section 3: Procedures
Topic 8: Major Hepatectomies
Topic 9: Minor Resections, resections on difficult segments, parenchyma sparing/anatomical segmentectomies
Section 4: Technique
Topic 10: Minimally invasive approaches, surgical devices, intraoperative staging and planning
Topic 11: Anatomic Major resection (Formal Right/left Hemi-hepatectomies)
Topic 12: Bleeding control/conversion
Section 5: Implementation
Topic 13: Surgeon/Center/Learning curves
Topic 14: Training/Registries

The consensus Guidelines was divided into several sections, each one divided into different topics (Table 8). In this consensus, the topics to be debated were broadened; expanding the field in terms of purely surgical techniques, indications, learning curves and patients' profile. An attempt was made in order to define the concepts of "high-risk patient" and expert surgeons.

A new concept of major hepatectomy was introduced; resection of posterior segments or complex resections were also considered major hepatectomies. Great importance was given to the development of courses and fellowship, which are considered of relevance for the training of young surgeons and for the safe expansion of the laparoscopic approach, taking place in high volume centres.

In these guidelines, it is defined that for lesions in the anterior and left lateral segments, the laparoscopic approach is considered to be the standard practice. Besides, complex resections and lesions in posterior segments should also be performed by laparoscopic approach.

These Clinical Guidelines provided statements and recommendations based on strong scientific evidence and were endorsed by both an expert committee and external validation committee.

1.4. Laparoscopic Liver Surgery in Hepatocellular Carcinoma

Liver resections for Hepatocellular carcinoma have been universally considered complex resections. The reason is that HCC is normally developed in cirrhotic patients with several adversities, such as thrombocytopenia, portal hypertension, ascites and greater probabilities of liver failure after resection.

The laparoscopic approach for HCC is especially difficult due to the difficult bleeding control in cirrhotic liver and the other reasons mentioned above. The laparoscopic approach began to be used in HCC resections with the intention of reducing postoperative complications and providing the benefits of this approach. Cirrhotic livers require a deeper knowledge of liver and laparoscopic surgery.

1.4.1. Literature review

The first reports are observed around the year 2000. These manuscripts consisted of a series of cases with a small number of patients. The inclusion criteria in the first reports were more strict: lesions in anteroinferior segments with a size smaller than 4-5 cm, and in which the tumor should not be located adjacent to any large vessels. Another requirement was the presence of a compensated liver function (Child A) (46).

The conclusions were that the laparoscopic approach could be considered a good option for the treatment of small or subcapsular HCC on well-compensated liver functions (53). This approach offers an acceptable alternative to the open resection with equivalent results regarding oncological-terms.

Furthermore, these series of cases, each time with a larger sample, showed how the laparoscopic approach improved the postoperative course of cirrhotic patients (54). Even considering surgery as a bridge therapy to liver transplantation, the laparoscopic approach could improve the surgical time (shorter operative time, less blood loss, shorter cold ischemia time).

With the widespread of laparoscopic approach, the number of published cases increased. The studies showed greater statistical power since comparative studies of both groups were also reported (open vs laparoscopic approach).

The first comparative reports consisted of small-sized series (less than 100) with a short follow-up period (55) (47) (56) (57). The results showed were homogeneous, where the laparoscopic approach offered clear benefits for HCC resections in cirrhotic livers vs the open approach. In 2014, some comparative studies with propensity score matching (PSM) analysis were published (58).

The PSM is a statistical matching technique that attempts to estimate the effect of a treatment or intervention by accounting for the covariates that predict receiving the treatment. PSM attempts to reduce the bias due to confounding variables that could be found in an estimate of the treatment effect

obtained from simply comparing outcomes among the ones that received the treatment versus those that did not. PSM homogenizes two groups based on similar variables in the studies: age, sex, number and size of lesions and degree of liver failure. In this way, this statistical tool avoids the confusion factors that could influence the results and homogenizes both groups to obtain more robust results (59).

Under these well-balanced comparative groups, the results were similar to the ones published in previous studies. LLR showed shorter hospital stay, less postoperative ascites (58), lower postoperative morbidity (60) (61), less median blood loss (62). Median overall survival rate and median disease-free survival rates were similar for both groups in the comparative studies.

A more complex level in comparative studies is the meta-analysis. Twaij in 2014 (63) analyzed several comparative studies in patients with proven cirrhosis. Operative time, blood loss, need of transfusions and histological tumor margins were evaluated. Postoperative measures included morbidity and mortality rates, length of stay in hospital, long-term survival rates and diseases free survival rate. This meta-analysis included 4 comparative cohort studies (64) (65) (66) (67) with a total of 420 patients (LLR=150, OR=270).

Authors reported that patients undergoing laparoscopic procedures had less blood loss, reduced risk of transfusion, better tumor resection margins, shorter length of stays in hospital and less postoperative morbidity. No statistically significant difference was reported across all studies with regards to both long-term survival and disease-free survival rates in the laparoscopic cohort vs OR.

A year later, Chen (68) published a systematic review and meta-analysis based on 7 retrospective trials (64) (65) (66) (67) (69) (70) (71) showing similar results. Patients undergoing LLR had wider tumor margin, less blood loss, less blood transfusion, less postoperative morbidity and less hospital stay while overall survival and disease-free survival rates were similar.

Leong published in the same year another interesting meta-analysis with a higher number of comparative studies, including a total of 17 retrospective cohorts studies. Authors showed that postoperative complications were significantly lower in laparoscopic groups.

Morise performed in 2015 (72) a systematic review of the current literature. The conclusions showed that the laparoscopic approach offered reduced blood loss, reduced postoperative complication rate and similar surgical margins. Regarding oncological terms, no significant difference was observed between the two approaches in overall survival or recurrence-free survival rates. The same author would report a meta-analysis of postoperative ascites (9 comparative studies) and postoperative liver failure (6 comparative studies) in cirrhotic patients undergoing laparoscopic vs open approach. In the analyses, the laparoscopic approach seemed to be associated with a reduced incidence of postoperative ascites (OR 0.26; 95% CI, 0.14-0.49; $p<0.0001$) and liver failure (OR 0.24; 95% CI, 0.14-0.49; $p=0.001$).

Over the past years, publications reporting patients undergoing laparoscopic resections for HCC have increased. Although there is no full statistical quality in the published studies, due to its retrospective nature, the literature currently available suggests a great benefit of the laparoscopic approach in these patients. With the current results, the laparoscopic approach for resections in cirrhotic patients should be considered as a feasible alternative.

1.4.2. Anatomical Laparoscopic resection

Surgical resection and liver transplantation represent the main therapeutic options with an intention-to-treat perspective for HCC. Liver resection is an alternative option and is now widely accepted as a potentially curative treatment for patients with HCC.

As mentioned above, the initial criteria for HCC liver resection were stricter: solitary tumors and very well-preserved liver functions, hepatic vein to portal system gradient ≤10 mm Hg or platelet ≥100.000/mL.

The complete resection of the entire tumor lesion, preserving enough liver remnant to avoid postoperative liver failure is the oncological principle for hepatic resection for HCC in cirrhotic livers (73). The importance of an anatomical resection results in obtaining a correct oncological margin, thus, reducing the risk of post-resection recurrence.

The first surgeon who described the area that should be resected for HCC as the subsidiary territory to the portal venous system in which the tumor is drained was Makuuchi (74). It was later described by Takasaki (75) through the Glissonian pedicle. This type of resection is considered as an anatomical resection (AR).

In contrast, there is the concept of non-anatomical resection (NAR). NAR is defined as the resection of a lesion regardless of the anatomical segment or section of the lobar anatomy and includes limited resection or enucleation (76).

There is a debate about the potential benefit of AR in HCC patients. It is considered that in AR, the territory removed includes a wider parenchymal area and possible satellite nodules. Most of the HCC develop on cirrhotic livers that have limited liver functions. The AR requires a greater resected parenchyma and a higher risk of developing liver failure.

Several studies have been conducted to compare the real benefits of AR and whether it provides better survival rate. There is another novel anatomical concept for defining the territory of the liver disease that must be resected in the HCC. This territory is called "cone unit" and was described by Takasaki (75).

This anatomical territory consists of portal tertiary branches that are tributary to the area where the HCC is located. For Takasaki, each segment consists of six to eight cone units. Following this concept, the liver as a whole is encompassed between 18 and 24 subsegments (which are designated as cone units) (77). The cone unit concept is universally considered as an anatomical resection.

This territory may be smaller than one Couinaud's segments (sub-segmentectomy) or involve more than one segment. This type of resection is considered precise from the anatomical and vascular point of view and seems to be related to a lower risk of complications such as ischemic areas in resection edges and bile leak (78). Both types of resections can be carried out by laparoscopic approach. In properly trained centres, LR should be considered via laparoscopic (1).

1.4.3. Theoretical benefits of laparoscopic approach for patients with Hepatocellular Carcinoma

Laparoscopic left lateral sectionectomy and minor laparoscopic liver resection are now considered standard approaches, especially for tumors located in the anterolateral segments of the liver (1).

Recent studies question whether there are benefits of using laparoscopy in complex resections such as posterosuperior segments. Xiao et al. (79) reported, through a case-control study, that LR for patients with HCC in these segments might offer the same oncologic outcomes as conventional procedures, being associated with advantages such as lower blood loss, fewer complications and shorter hospital stay.

Improved laparoscopic techniques, better visualization of the operative field using a flexible laparoscope, and routine use of a laparoscopic ultrasonic surgical aspiration devices for transecting the deeper portion of the liver parenchyma have allowed laparoscopic resection to be performed in more complex cases.

Regarding short-term results, operative time seems to be similar between both approaches (due to the improvement with the progression of the learning curve). Blood loss and need of transfusions is reduced in patients undergoing LLR compared to OLR. Postoperative morbidity is significantly lower in LLR group (80) (less ascites, less infection, less chest complication, less pleural effusion and less abdominal wall complications).

In general, patients undergoing OLR had significantly longer hospital stay than LLR patients

(81). Postoperative mortality is similar in both groups. Regarding long-term and oncological results, tumor margins were similar in both groups. In some studies it was significantly wider in LLR than in OLR (60); this could be explained by two factors: tumor size in OLR group tends to be greater and usually closer to vessels and hepatic pedicle.

Overall survival and disease-free survival rates are similar in both groups. In different studies, disease-free survival seems is better in LLR group than in OLR (82). This might be because patients in LLR groups tend to have smaller tumour size and microscopic vascular invasion was more frequent in the OLR group.

Therefore, selection bias might be present in these studies. According to the previous results. In general, short-term outcomes are favourable to laparoscopic approach (80) (83) (fewer complications), whenever it is performed in expert centres.

Long-term outcomes and survival and disease-free survival rates are similar in both groups. The last meta-analysis reported by Twaij et al. (63) suggests that LLR for HCC in cirrhotic livers is safe and might offer improved patient outcomes. LLR seems to be associated with better short-term outcomes compared to OLR in HCC liver resection. Long-term oncological outcomes could be comparable in both groups.

These results should be handled with care, as they are all based on selected patients, in the setting of non-randomized comparative retrospective studies with selection biases mainly due to tumour characteristics. However, nowadays there have been many meta-analyses, retrospective studies and case-matched studies with propensity score matching comparing the open and laparoscopic approach proving these results and improving their evidence level.

2. HYPOTHESIS

2.1. Hypothesis

Null Hypothesis: Laparoscopic surgery is not inferior to open surgery in the management of Hepatocellular carcinoma.

Alternative Hypothesis: Laparoscopic hepatic surgery offers advantages compared to open surgery in the management of Hepatocellular carcinoma.

3. OBJECTIVES

3.1. Objectives

1. To amalgamate, weigh and summarize the current evidence literature by SIGN methodology for the development of the European Guidelines Meeting on Laparoscopic Liver Surgery and to elaborate consistent and evidence-based statements in the application of minimally invasive approach for the management of hepatocellular carcinoma.
2. To assess the distribution of available studies with regards to disease stage and resection type and perform secondary subgroup meta-analyses by grouping like studies in order to increase the level of evidence for specific disease stages and resection types (Solitary tumor, Child-Pugh A resections, minor-only liver resections, Major-only liver resections and Combined resections).
3. To expose the current evidence regarding the short-term outcomes as rate of complications, blood loss, transfusion rate and postoperative hospital stay for each group of study
4. To evaluate if considering severe morbidity, including liver-specific posthepatectomy liver failure and 90-days mortality, laparoscopic approach offers benefits against the open. To evaluate if laparoscopic approach have an impact on long-term outcomes considering overall survival and disease-free survival.
5. To demonstrate whether laparoscopic approach for the treatment of hepatocellular carcinoma may be considered as the first option and in which cases it could be considered as standard of practice.

4. PATIENTS AND METHODS

4.1. Study design and search strategy

In the context of the European Guidelines Meeting on Laparoscopic Liver Surgery (EGMLLS) held in Southampton, UK, from 9 to 11 February 2017, an updated meta-analysis was prepared in which five submeta-analyses were performed after assessing the patterns of all available studies comparing the laparoscopic and open approaches in the management of HCC (84).

The systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (85). PRISMA is an evidence-minimum set of items for reporting in systematic reviews and meta-analyses (Appendix 1) *www.prisma-statement.org.*

PRISMA focuses on the reporting of reviews evaluating randomized trials, but can also be used as a basis for reporting systematic reviews of other types of researchs, particularly evaluations of interventions. A systematic review using Ovid Medline and Pubmed was undertaken in July 2016 and repeated in January 2017 to review all the existing literature.

The Pubmed, Embase, Cochrane Library, and Web of Science electronic databases were searched using the following search strategy: ((hepatocellular [Title] OR HCC) AND (laparoscopic [Title] OR laparoscopy [Title] OR minimally [Title] OR hybrid [Title])) and their associated combinations of controlled vocabulary (Medical Subject Heading [MeSH]) terms.

4.2. Study selection and inclusion criteria

The inclusion criteria were studies conducted in humans published in English language. All the included studies were comparative studies between groups under open versus laparoscopic approach published in the last 15 years (Table 9). Reviews, case reports and other observational studies were excluded. In addition studies comparing radiofrequency, chemoembolization, robotic or hybrid surgery were also excluded.

A huge emphasis was made in the identification of duplicate cases. This process was performed by matching both author names and publication centres. Once the full-text version was obtained, two reviewers performed the screening stages independently. Disagreements were resolved after consultation with a third reviewer. These reviewers reviewed the final included articles to confirm they met the inclusion criteria.

Table 9. Exclusion and inclusion criteria.

Inclusion criteria	Exclusion criteria
Human studies	Animal / Experimental studies
Comparative studies	Review / Editorial / Case report / Letter
English language	Radiofrequency / TACE
Only laparoscopic versus open	Liver transplant involved
Only the last 15 years	Robotics / Hybrid cases
Duplicated data, most recent included	Adenomas or non-confirmed HCC

All manuscripts were screened to find out if subgroup analyses could be obtained. A secondary screening was performed to find out if a reasonable number of series could be achieved for a meta-analysis in the subsequent groups: major and minor resections, solitary tumors and Child-Pugh A tumors.

4.3. Definitions

Once the literature search has been carried out, the next step was to establish the concepts that are going to be taken into account in order to have these concepts understood in a universal way. Considering the aims of our study, the following definitions and patterns were considered:

- The type of resection was defined according to the criteria established in the First Consensus that was held in Louisville (50). For this, the structure described by Couinaud is followed. Minor resections involve two or fewer Couinaud segments and major resections involve three or more continuous Couinaud segments.

- Each manuscript was assessed to establish if results reported could be applicable to more than one of the subgroups. If so, the results were separated and individually analysed within their subgroups.
- There is a group of resections in which a specific type is not performed. Therefore, for our study we consider them as combined resections. These cases might not be grouped in any of the defined subgroups and will be excluded for the subgroup analysis.

4.4. Variables and End-Points

The variables analysed in each manuscript as well as the endpoint variables are universally established according to the reviewed manuscripts in order to lose the minimum number of cases in the literature.

- Short-term outcomes (intraoperative parameters): operative time (minutes), operative blood loss (mL) and the number of patients requiring blood transfusion (%).
- Short-term outcomes (postoperative parameters): total number of early (<30 days), complications (%), duration of postoperative hospital stay (days), mean resection margin (mm), post-hepatectomy liver failure (PHLF) and perioperative (30-day, 90-day, or undefined) mortality.
- Long-term outcomes. 1-, 3- and 5-year overall survival (OS) rate; 1-,3-, and 5-year disease-free recurrence rate.

4.5. Quality analysis of the studies

The manuscripts included in the meta-analysis are subjected to a double-check quality analysis. That assessment was performed first under the Scottish Intercollegiate Guidelines Network (SIGN) methodology criteria and then in accordance with the Newcastle-Ottawa Quality Assessment Scale (NOS) for cohort and case-control studies (Ottawa Hospital Research Institute).

This double assessment of each manuscript included is performed to reduce the risk of biases and thus enhance the quality of their results.

4.5.1. SIGN Methodology

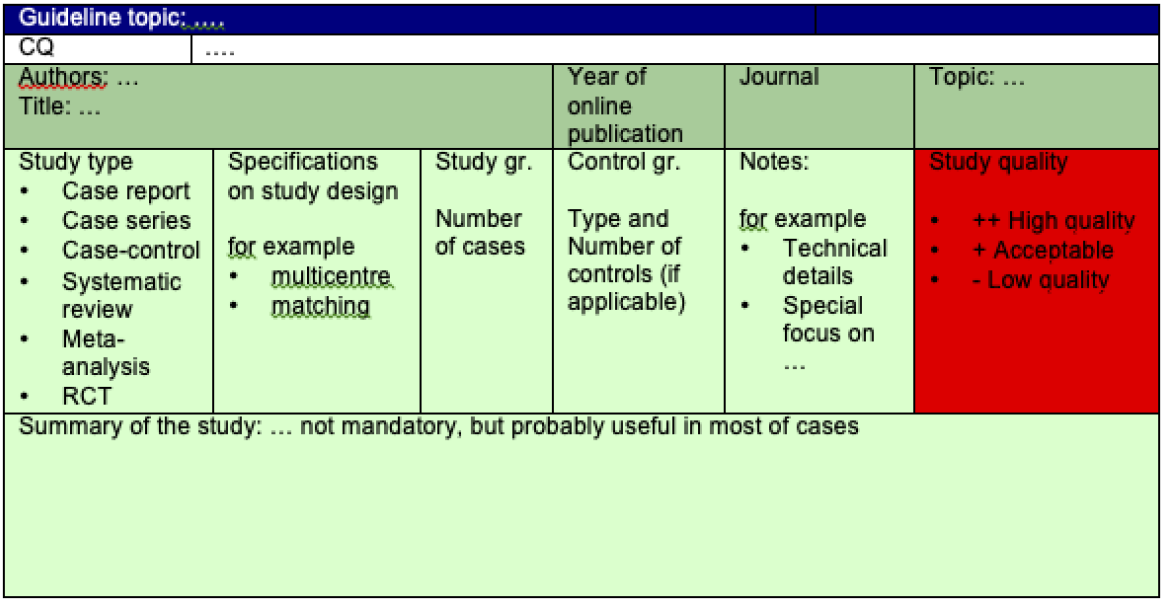
The Scottish Intercollegiate Guidelines Network (SIGN) was described by Harbor in 1993 (86). The SIGN methodology has been the basis of the first national programs for the elaboration of Clinical Practice Guidelines (CPG).

Table 10. Key to evidence statements and forms of recommendations. Methodology procedure for Developing Recommendations By SIGN Guidelines.

Levels of evidence	
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews, or RCTs with a low risk of bias
1-	Meta-analyses, systematic reviews, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case-control or cohort studies High-quality or cohort studies with a very low risk of confounding or bias and a high probability that the relationship is causal
2+	Well-conducted case-control or cohort studies with a low risk of confounding or bias and a moderate probability that the relationship is causal
2-	Case-control or cohort studies with a high risk of confounding or bias and a significant risk that the relationship is not causal
3	Non-analytic studies, eg case reports, case series
4	Expert opinion

The SIGN methodology consists of a manuscripts evaluation process that guarantees high quality in the selection process. These checklists are available for systematic reviews and meta-analyses, randomized controlled trials, cohort studies, case-control studies, diagnostic studies, and economic studies. The evaluation of the quality of manuscripts gives rise to the qualification of the study as: ++High quality, +Acceptable and –low quality (Table 10).

Once the first step is completed, the evidence level on the topic is produced based on the quality of the available literature assessed at the previous step. The next step, once the evidence tables of each manuscript have been made, is to produce recommendations according to the evidence found in each one of them.



Guideline topic:.....					
CQ	....				
Authors: ... Title: ...			Year of online publication	Journal	Topic: ...
Study type • Case report • Case series • Case-control • Systematic review • Meta-analysis • RCT	Specifications on study design for example • multicentre • matching	Study gr. Number of cases	Control gr. Type and Number of controls (if applicable)	Notes: for example • Technical details • Special focus on ...	Study quality • ++ High quality • + Acceptable • - Low quality
Summary of the study: ... not mandatory, but probably useful in most of cases					

Figure 8. Summary of Findings (SoF) example.

The structure of this table is perfectly designed. In the first part, the main topic of the clinical guideline and the clinical question under study should be explained. Later on, the bibliographic information of the article is described: Authors, journal and year of publication. Within the evaluation of the paper, the type of comparative study must be described (case-control, cohort, meta-analysis).

There are two sections in which the characteristics and number of cases and controls must be shown (PSM study, describe the variables on which this analysis is based). Another section is for the notes where the aspects of the design of the study must be described (follow up time, bias found or other data that could be important for its evaluation).

The larger section is dedicated to performing a brief summary, results, limitations and conclusions of the study. And finally, the SIGN classification score of each of them (Figure 8).

According to the SIGN methodology, recommendations are formulated in order to produce appropriate conclusions (Table 11).

Balancing all the issues described is complex and presents a challenge to any guideline group. The outcome of the decision-making process is to produce a recommendation that is rated as either "strong" or "conditional".

High quality evidence from well conducted studies should lead to a strong recommendation, but relating the trial populations to the target population of a guideline and taking into account issues of cost and patient acceptability might lead to a recommendation that is much weaker than first thought.

Equally, there will be circumstances where the evidence is flawed but there are few or no

downsides to the treatment and the clinical importance of the topic is such that a strong recommendation is justifiable.

Table 11. Forms of recommendation by SIGN Methodology

Forms of recommendation	
Judgment	**Recommendation**
Undesirable consequences clearly outweigh desirable consequences	Strong recommendation against
Undesirable consequences probably outweigh desirable consequences	Conditional recommendation against
Balance between desirable and undesirable consequences is closely balanced or uncertain	Recommendation for research and possibility conditional recommendation for use restricted to trials
Desirable consequences probably outweigh	Conditional recommendation for undesirable consequences
Desirable consequences clearly outweigh	Strong recommendation for undesirable consequences
Good Practice points	
Recommended best practice based on the clinical experience of the guideline development group	

4.5.2. Newcastle-Ottawa Methodology

The Newcastle-Ottawa Scale (NOS) was developed to evaluate the quality of non-randomized studies seeking to incorporate quality assessments in meta-analysis interpretation of the results obtained. The NOS evaluates the quality from the content, design and ease of use in the interpretation of the meta-analysis. It is composed of eight items, divided into three dimensions (comparability, selection, type of study) of the transversal study or case-control.

The apparent validity and content was established based on a critical review of the items by specialists in the area. Stars awarded for each quality item serve as a quick visual assessment. Stars are awarded so the studies with the highest quality are awarded up to nine stars (Table 12 y 13). The method was developed as a collaboration between the University of Newcastle, Australia, and the University of Ottawa, Canada using a Delphi process to define variables for data extraction. The scale was then tested on systematic reviews and furtherly refined (87).

The criteria for "representativeness of cases" was the consideration of consecutive, or representative series of cases without potential selection bias. Specifically, no star was given if the cases included were not matched by the year of inclusion (due to potential selection bias) and/or different surgeons and/or an inclusion period >10 years (due to potential technical bias).

Similarly, an equal distribution of type and severity of underlying liver disease was an exclusion criterion that was given a star. For the "control for impact factor" rating, two stars were given if laparoscopic and open cases were matched by age, sex, American Society of Anesthesiologists (ASA) score, body mass index, type of resection, Child-Pugh score, and number and size of the lesions. If any of these factors were not specifically mentioned or were not correctly matched, only one star was given. If two or more of these factors were not correctly matched or were not mentioned, no stars were given.

4.6. Statistical Methodology

4.6.1. Methodology for the estimation of the mean and deviation

To perform meta-analyses, means and standard deviations (SDs) were needed, and estimations of means and SDs were performed to avoid discarding important studies. According to a recent publication from Wan et. al (94), in the event that a manuscript reported data in different measures other than mean and SD, different scenarios were considered.

A number of studies reported the study using the median, the minimum and maximum values, and/or the first and third quartiles. Four possibilities are available in all paper (Figure 9). The perfect situation is the articles in which the variables are expressed in mean and SD.

Table 12. Newcastle-Ottawa Scale for Cohorts Studies

Newcastle-Ottawa Quality Assessment Scale: COHORT STUDIES

Selection (★★★★) Comparability (★★) Outcome (★★★)

Selection

1. Representativeness of the exposed cohort
   a. Truly representative of the average _____(describe) in the community (★)
   b. Somewhat representative of the average _____ in the community (★)
   c. Selected group of users eg nurses, volunteers
   d. No description of the derivation of the cohort
2. Selection of the non exposed cohort
   a. Drawn from the same community as the exposed cohort (★)
   b. Drawn from a different source
   c. No description of the derivation of the non exposed cohort
3. Ascertainment of exposure to implants
   a. Secure record (eg surgical records) (★)
   b. Structured interview (★)
   c. Written self-report
   d. No description
4. Demonstration that any outcome of interest was not present at the start of the study
   a. Yes (★)
   b. No

Comparability

1. Comparability of cohorts on the basis of the design or analysis
   a. Study controls for _____ (select the most important factor) (★)
   b. Study controls for any additional factor (This criterion could be modified to indicate specific control for a second important factor) (★)

Outcome

1. Assessment of outcome
   a. Independent blind assessment (★)
   b. Record linkage (★)
   c. Self-report
   d. No description
2. Was follow up long enough for outcomes to occur
   a. Yes (select an adequate follow-up period for the outcome of interest) (★)
   b. No
3. Adequacy of follow up of cohorts
   a. Complete follow up-all subjects accounted for (★)
   b. Subjects lost to follow up unlikely to introduce bias-small number lost >__% (select an adequate %) follow up, or description of those lost (★)
   c. Follow up rate <__% (select an adequate %) and no description of those lost
   d. No statement

Table 13. Newcastle-Ottawa Scale for case-control Studies

Newcastle-Ottawa Quality Assessment Scale: CASE-CONTROL STUDIES

Selection (★★★★) Comparability (★★) Exposure (★★★)

Selection

1. Is the case definition adequate?
   a. Yes, with independent validation (★)
   b. Yes, eg record linkage or on self-reports
   c. No description
2. Representativeness of the cases
   a. Consecutive or obviously representative series of cases (★)
   b. Potential for selection biases or not stated
3. Selection of controls
   a. Community controls (★)
   b. Hospital controls
   c. No description
4. Definition of controls
   a. No history of disease (endpoint) (★)
   b. No description of source

Comparability

1. Comparability of cases and controls on the basis of the design or analysis
   a. Study controls for _____(select the most important factor) (★)
   b. Study controls for any additional factor (this criterion could be modified to indicate specific control for a second important factor) (★)

Exposure

1. Ascertainment of exposure
   a. Secure record (eg surgical records) (★)
   b. Structured interview, blind to case/control status (★)
   c. Interview not blinded to case/control status
   d. Written self-report or medical record only
   e. No description
2. Same method of ascertainment for cases and controls
   a. Yes (★)
   b. No
3. Non-response rate
   a. Same rate for both groups (★)
   b. Non-respondents described
   c. Rate different and no designation

In this case, there is no need to perform any calculation to perform the meta-analysis. The scenario 2 is the situation in where the variables are expressed by mean and 95% CI. In this case mean and CI must be converted to median and range (Scenario 3) in order to apply the formula of Wan to obtain the mean and SD. And the last possibility (Scenario 4) is when the variables are expressed in Median and interquartile range (IQR). In this case applying again the expressed formula mean and SD are obtained.

For the meta-analysis, we decided to perform calculations only if at least three series could be identified for each variable, avoiding results derived from analyses of two reports.

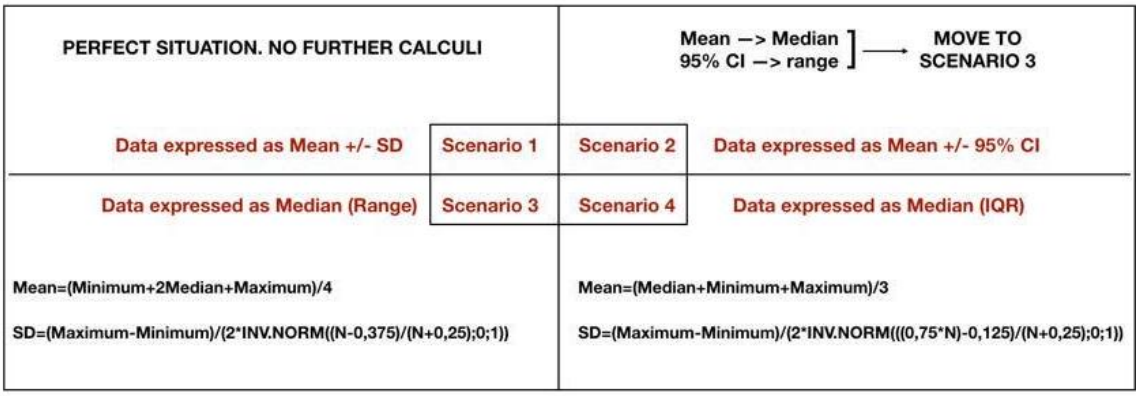


Figure 9. Different Scenarios to obtain mean and standard desviation for meta-analysis.

4.6.2. Determination of the heterogeneity of the samples

Heterogeneity I^2 test

An important point in the methodology is to quantify the heterogeneity between the studies included for the meta-analysis, its magnitude derives not only the method used to combine the individual results but also the validity of the global conclusions.

One of the aspects of heterogeneity, the one related to clinical or biological differences between studies and the differences in procedures, is first of all a methodological problem, since it will be necessary to decide whether the differences between the studies, which always exist, allow or not to combine them, independently of the results that have been obtained in them.

Therefore, the identification of the heterogeneity is prior to the execution of the meta-analysis. The statistical heterogeneity tries to quantify the variability of the result measured in the different studies with respect to the average global result, and determine whether that variability is higher than what would be expected by pure chance.

The standard heterogeneity test used was the I-square statistic. Based on the method reported by Der Simonian and Laird (88), substantial significance was set when the p-value was <0.10 and a random-effects model was used (89).

The I^2 parameter indicates the proportion of the variation among studies with respect to the total variation, so, the proportion of the total variation that is attributable to the heterogeneity, as follows:

$$I^2 = \frac{r^2}{r^2 + \sigma^2}$$

An I-square value of <25% was defined to represent low heterogeneity, between 25 and 50% was defined as moderate heterogeneity, and >50%

was defined as high heterogeneity. If I^2 <25%, studies are regarded as homogeneous and the fixed effect model of meta-analysis can generally be used. If I^2>75% then, the heterogeneity is very high, and one should use a random effect model for meta-analysis.

A random-effects model takes into account that there might be other unpublished studies, overlooked in the systematic literature search, or to be undertaken in the future which were not included in the meta-analysis at hand (90).

Funnel plots

Meta-analysis results are commonly displayed graphically as "forest plots". Publication bias was also assessed visually using a funnel plot for standard error by effect size. Each calculation for every group has a specific funnel plot. In the funnel plot, the X-axis represents the mean result (that might be an odds or risk ratio, or a percentual difference) and the Y-axis shows the sample size or an index of precision.

The symmetry of the plot might vary depending on whether the sample size or inverse standard error is used as an index of precision. The points that represent each mean value are widely spread at the base and narrow as they move to the top, thus resembling an inverted funnel or a fir tree.

The basis of assessing bias is that if all the studies are given random assessments of the same unbiased mean value, the plot should be symmetrical. If the studies are biased, for example, by having too few small studies with positive results and large effect sizes, then the funnel plot becomes asymmetrical with a deficit near the bottom (91).

4.6.3. Selection of the statistical test according to heterogeneity

Data that was not significantly heterogeneous (p>0.1) was calculated using a fixed-effects model using the Mantel-Haenszel method (92). OpenMEE software, based on Open MetaAnalyst Sotware, was used for statistical analyses (93).

Analyses were performed using log odds ratios (OR) with 95% confidence intervals (CIs) for dichotomous variables, and weighted mean differences (WMD) with 95% CIs for continuous variables.

For those dichotomous variables in which any observed value was 0, the calculation of the OR was not possible, so rate differences were used (94).

In cases where a high heterogeneity (I^2) was obtained, the test used will be a random-effects model to obtain a lower degree of bias and greater statistical significance. For variables with low heterogeneity (I^2<25), we assume that the sample is distributed homogeneously and therefore, the fixed-effect model will be used to obtain less biased results.

5. RESULTS

5.1. Flow chart and choice of studies

A search through PubMed, EMBASE and Google Scholar databases was performed to identify all studies, case series and comparative studies analysing LLR compared with open resection for HCC patients. Keywords were "Hepatocellular" and "HCC", "laparoscopic" or "laparoscopy" or "minimally" or "hybrid" (hepatocellular[Title] OR HCC[Title]) AND (laparoscopic[Title] OR laparoscopy[Title] OR minimally[Title] OR hybrid[Title]). Our search was restricted to human studies published during the last fifteen years.

Only comparative studies were included, therefore, case series, case reports and other kinds of studies were excluded. Robotic manuscripts and radiofrequency treatments were also excluded. For meta-analysis, we included only manuscripts with endpoints short-term, long-term and oncological comparative outcomes between LLR and OLR.

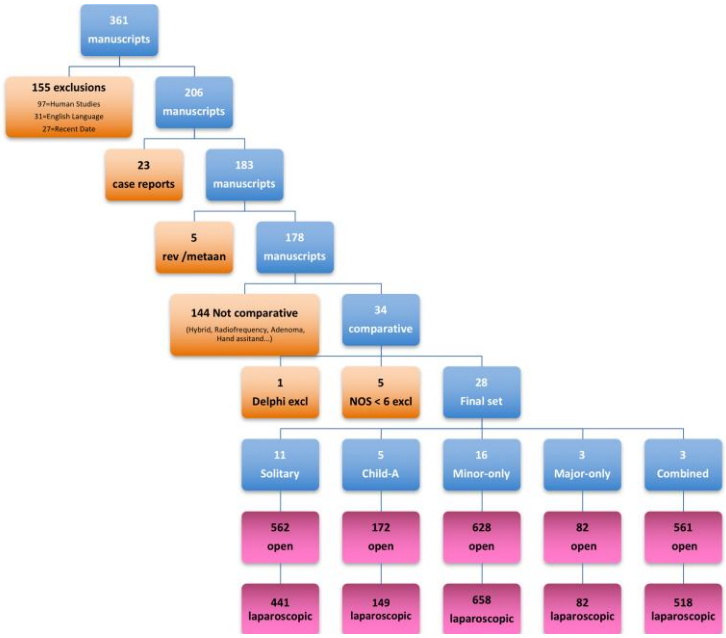


Figure 10. Flow chart and choice of study

From the initial 361 manuscripts identified in the initial search, 34 comparative studies remained after the inclusion and exclusion criteria were applied (Figure 10). Six manuscripts (95) (79) (96) (97) (55) (98) did not reach a mínimum requirement of acceptable quality (measured by SIGN scoring) or 6 points (measured by NOS) and were subsequently discarded (Table 14). Resulting in 28 manuscripts being finally considered for the systematic review and meta-analysis.

Five of these 28 manuscripts were specific to patients with Child-Pugh A cirrhosis [321 cases] (81) (59) (58) (66) (99), 16 focused on minor resections [1286 cases] (47) (61) (58) (64) (65) (66) (69) (71) (99) (100) (101) (102) (103) (104) (105) (106), three focused on major resections [164 cases] (80) (81) (83) and 10 focused on solitary tumors [1003 cases] (47) (56) (57) (59) (99) (101) (107) (108) (109) (110). The remaining three manuscripts (comparing 1079 cases) could not be individually classified as they did not divide among specific HCC subgroups and, hence independent results could not be obtained (60) (62) (82); these were analyzed as "combined" resections.

5.2. Quality analysis of literature

Thirty-four manuscripts were obtained after verifying the inclusion and exclusion criteria. The next step was to perform an evaluation according to the SIGN Methodology for developing recommendations and Newcastle-Ottawa assessment. Six manuscripts (95) (79) (96) (97) (55) (98) did not reach a mínimum requirement of acceptable quality (measured by SIGN scoring) or 6 points (measured by NOS) and were subsequently discarded (Table 14), resulting in 28 manuscripts being finally considered for the systematic review and meta-analysis. All baseline results are depicted in Table 15.

5.2.1. Quality results based on SIGN Methodology (Appendixes 2 and 3)

According to the criteria established by SIGN Methodology (Appendixes 2 and 3), the manuscript published by Hu (96) does not meet the mínimum items obtaining a "Low" Classification, being discarded. This paper describes a retrospective evaluation of a cohort of patients who underwent laparoscopic hepatectomy at a single centre.

The aim was to investigate the effects of laparoscopic hepatectomy for the treatment of HCC. The limitations of this article were the small sample size, only performed one control per case. The recurrence and survival rate were low (although there were no significant differences) and did not show how much percentage of patients completed follow up at 5 years. The checklist evaluation for the cohort studies has a low score.

There are several questions that are not resolved with the manuscript of Hu. For example, in the section for the selection of subjects, for the ítem related to whether the study indicates how many people asked to take part on the study, actually did so, for each of the groups being studied the answer is always not.

Besides, for the ítem related to the likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis the answer is not. An important objective that does not comply with this study is the control of possible confounding factors, which results in low power of evidence study and with a high level of biases that could alter the results. Additionally, confidence limits are not provided in this paper. Confidence limits are the preferred method for indicating the precision of statistical results and can be used to differentiate between an inconclusive study and a study that shows no effect. In this case, a single value is reported with no assessment of precision, so it should be treated with extreme caution. Therefore, this study is considered unacceptable and is discarded for the meta-analysis.

5.2.2. Quality results based on Newcastle Ottawa Scoring system

According to the Newcastle Ottawa scale, the manuscripts published by Lee (95), Xiao (79), Ker (97), Aldrighetti (55) and Endo (98) do not meet the mínimum items for obtaining a score higher or equal than 7 stars. As observed in Table 14 and is explained in the methodology section, there is a mínimum of items that each article must meet to pass the NOS evaluation.

Most of these articles have a deficiency within the case and control selection (there are not enough representative samples or the way to select them is biased). In the case of Ker (97), Aldrighetti (55) and Endo (98) a deficiency can also be observed in the comparability section: a statement that is not fulfilled in these articles is that either exposed and non-exposed individuals must be matched in the design and/or confounders must be adjusted for the analysis. Statements of no differences between groups or that differences were not statistically significant are not sufficient for establishing comparability.

5.3. Summary of findings (Appendix 4)

After analyzing every manuscript and performing individual checklists, all of them are summarized into a "Summary of findings proforma" (SoF). (APPENDIX 4). By doing so, the experts obtained a brief summary of them and a quick visualization to evaluate the reason why some of them are discarded.

Table 14. Overall quality analysis from all comparative studies including Newcastle-Ottawa and SIGN scores. Red marked studies were the discarded ones because of NOS <7 stars or Low scoring in the SIGN analysis.

Author Country	Year	Nlap	Nopen	Etiology	Conversion	Quality assessment by Newcastle-Ottawa Scale									
						Selection				Comparability	Exposure			Quality judgment (máximum 9 stars)	SIGN
						Adequate definition of cases	Representa-tiveness of cases	Selection of controls	Definition of controls	Control for important factor	Ascertain-ment of exposure	Same method to ascertain for cases and controls	Non-response rate		
CHILD-A															
Zhang China	2016	20	25	HCC	-	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable
Ahn Daegu-Korea	2014	52 (51)	150 (51)	HCC	Were excluded	★	★	-	★	★★	★	★	★	★★★★★★★★	++ High
Kim Seoul-Korea	2014	29	29	HCC	23,3%	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
Truant Lille-France	2011	36	53	HCC	7(19,4%)	–	–	–	★	★★	★	★	★	★★★★★★	+ Acceptable
Lee Hong Kong-China	2011	33	50	HCC	6(18,2%)	–	–	–	★	★	★	★	★	★★★★★	+ Acceptable
Laurent Creteli-France	2003	13	14	HCC	2(15%)	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable

Table 14. (Cont) Overall quality analysis from all comparative studies including Newcastle-Ottawa and SIGN scores. Red marked studies were the discarded ones because of NOS <7 stars or Low scoring in the SIGN analysis.

Author Country	Year	Nlap	Nopen	Etiology	Conversion	Quality assessment by Newcastle-Ottawa Scale									
						Selection				Comparability	Exposure			Quality judgment (máximum 9 stars)	SIGN
MINOR ONLY															
Sposito Italy	2016	43 (43)	226 (43)	HCC	Were excluded	★	★	-	★	★★	★	★	★	★★★★★★★★	++ High
Zhang China	2016	31	33	HCC	0 (0%)	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable
Luo Chengdu-China	2015	53	53	HCC	Were excluded	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable
Beppu Kumamoto-Japan	2015	89 (52)	180 (52)	HCC	2 (2.2%)	★	★	-	★	★	★	★	★	★★★★★★★	++ High
Xiao China	2015	41	86	HCC	3 (7.32%)	-	★	-	★	★	★	★	★	★★★★★	++ High
Cheung Hong-Kong-China	2015	24	29	HCC	-	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable
Yamashita Fukuoka-Japan	2014	63	99	HCC	-	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable
Memeo Creteil-France	2014	45	45	HCC	0	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
Kim Seoul-Korea	2014	29	29	HCC	23,3%	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
Kanazawa Osaka-Japan	2013	28	28	HCC	5/23 hybrid (21,73%)	–	–	–	★	★★	★	★	★	★★★★★★	+ Acceptable
Cheung Hong Kong-China	2013	32	64	HCC	6 hand-assist (18,8%)	–	–	–	★	★★	★	★	★	★★★★★★	+ Acceptable
Kobayashi Osaka-Japan	2013	24	27	HCC	-	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable
Hu Jiangsu-China	2011	30	30	HCC	-	-	★	-	★	★	★	★	★	★★★★★★	- Low

Table 14. (Cont) Overall quality analysis from all comparative studies including Newcastle-Ottawa and SIGN scores. Red marked studies were the discarded ones because of NOS <7 stars or Low scoring in the SIGN analysis.

Author Country	Year	Nlap	Nopen	Etiology	Conversion	Quality assessment by Newcastle-Ottawa Scale									
						Selection				Comparability	Exposure			Quality judgment (máximum 9 stars)	SIGN
Truant Lille-France	2011	36	53	HCC	7(19,4%)	–	–	–	★	★★	★	★	★	★★★★★★	+ Acceptable
Lee Hong Kong-China	2011	33	50	HCC	6(18,2%)	–	–	–	★	★	★	★	★	★★★★★	+ Acceptable
Ker Kaohsiung-China	2011	116	208	HCC	6 (5.2%)	–	–	–	★	–	★	★	★	★★★★	+ Acceptable
Aldrighetti Milan-Italy	2010	16	16	HCC	1(6,25%)	–	–	–	★	–	★	★	★	★★★★	+ Acceptable
Endo Oita-Japan	2009	10	11	HCC	Lap-assisted	–	–	–	★	–	★	★	★	★★★★	+ Acceptable
Belli Naples-Italy	2007	23	23	HCC	1(4,3%)	–	–	–	★	★★	★	★	★	★★★★★★	++ High
Kaneko Tokyo-Japan	2005	30	28	HCC	3,3%	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
Laurent Creteli-France	2003	13	14	HCC	2(15%)	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
Shimada Fukuoka-Japan	2001	17	38	HCC	0	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
MAJOR															
Zhang China	2016	20	25	HCC	-	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable
Komatsu France	2016	38	38	HCC	-	-	★	-	★	★★	★	★	★	★★★★★★★	+ Acceptable
Cho Seoul-Korea	2015	24	19	HCC	3 (12.5%)	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable

Table 14. (Cont.) Overall quality analysis from all comparative studies including Newcastle-Ottawa and SIGN scores. Red marked studies were the discarded ones because of NOS <7 stars or Low scoring in the SIGN analysis.

Author Country	Year	Nlap	Nopen	Etiology	Conversion	Quality assessment by Newcastle-Ottawa Scale								
						Selection				Comparability	Exposure			Quality judgment (máximum 9 stars)	SIGN
SOLITARY TUMORS															
Luo Chengdu-China	2015	53	53	HCC	Were excluded	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable
Xiao China	2015	41	86	HCC	3 (7.32%)	-	★	-	★	★	★	★	★	★★★★★	++ High
Ahn Daegu-Korea	2014	52 (51)	150 (51)	HCC	Were excluded	★	★	-	★	★★	★	★	★	★★★★★★★★	++ High
Kim Seoul-Korea	2014	70	76	HCC	6 (8.57%)	★	★	-	★	★★	★	★	★	★★★★★★★★	++ High
Ai Putian-China	2013	97	178	HCC	9,3%	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
Hu Jiangsu-China	2011	30	30	HCC	-	-	★	-	★	★	★	★	★	★★★★★★	- Low
Kim Gwangju-Korea	2011	26	29	HCC	3 (10.3%)	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable
Nguyen Pittsburgh-USA	2011	17	20	HCC	-	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
Ker Kaohsiung-China	2011	116	208	HCC	6 (5.2%)	–	–	–	★	–	★	★	★	★★★★	+ Acceptable
Tranchart Paris-France	2010	42	42	HCC	2 (4.7%)	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
Aldrighetti Milan-Italy	2010	16	16	HCC	1(6,25%)	–	–	–	★	–	★	★	★	★★★★	+ Acceptable
Endo Oita-Japan	2009	10	11	HCC	Lap-assisted	–	–	–	★	–	★	★	★	★★★★	+ Acceptable
Lai Chai Wan-HongKong	2009	25	33	HCC	1(4%)	-	★	-	★	★	★	★	★	★★★★★★	+ Acceptable

Table 14. (Cont.) Overall quality analysis from all comparative studies including Newcastle-Ottawa and SIGN scores. Red marked studies were the discarded ones because of NOS <7 stars or Low scoring in the SIGN analysis.

Author Country	Year	Nlap	Nopen	Etiology	Conversion	Quality assessment by Newcastle-Ottawa Scale									
						Selection				Comparability	Exposure			Quality judgment (máximum 9 stars)	SIGN
Kaneko Tokyo-Japan	2005	30	28	HCC	3,3%	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
Laurent Creteli-France	2003	13	14	HCC	2(15%)	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
Shimada Fukuoka-Japan	2001	17	38	HCC	0	–	★	–	★	★	★	★	★	★★★★★★	+ Acceptable
COMBINED															
Takahara Japan	2015	436 (387)	2969 (387)	HCC	25 (6.5%)	★	★	-	★	★★	★	★	★	★★★★★★★★	++ High
Han Seoul-Korea	2015	232 (88)	157 (88)	HCC	8 (9.1%)	★	★	-	★	★	★	★	★	★★★★★★★	++ High
Lee Toront-Canada	2015	43	86	HCC	6(14%)	-	★	-	★	★	★	★	★	★★★★★★	++ High

Table 15. Baseline descriptive results from all eligible studies.

CHILD A														
Author Country	**Year**	**N lap N open**	**Complications**	**Blood loss**	**Transfusions**	**Operative time**	**Hospital stay**	**Mean resection margin**	**1y survival**	**3y survival**	**5y survival**	**1y DFS**	**3y DFS**	**5y DFS**
Zang China	2016	20	0	180±20,5	0	143±36	7±1	21,2±3,7	20			20		
		25	10	350±45,3	0	137±30	12±2	22±3,6	25			25		
Ahn Daegu-Korea	2014	51	3	350±432	3	211±131	8,2±4,6	17±17			41			35
		51	5	355±312	5	202±51	12,3±8,6	13±8			44			28
Kim Seoul-Korea	2014	29	4	483 ±820	1	210±82	7,7±2,9	11,1±6,7	29	29	27	24	18	16
		29	11	261±301	0	203±51	13,4±7,4	10±7,5	28	27	25	24	18	12
Truant Lille-France	2011	36	9	452±442	1	193±104	6,5±2,7	9,5±2,8			25			13
		53	19	447±450	2	216±89	9,5±4,8	8,6±1,7			24			18
Laurent Creteli-France	2003	13	4	620±130	1	267±79	15,3±8,6	9±2,5		12			6	
		14	13	720±240	4	182±57	17,3±18,9	8,8±1,3		8			6	

Table 15. (Cont.) Baseline descriptive results from all eligible studies.

MINOR-ONLY														
Author Country	**Year**	**N lap N open**	**Complications**	**Blood loss**	**Transfusions**	**Operative time**	**Hospital stay**	**Mean resection margin**	**1y survival**	**3y survival**	**5y survival**	**1y DFS**	**3y DFS**	**5y DFS**
Sposito Italy	2016	43	8				10,5±6,86	8,25±4,34		32,2	16,3		17,6	10,75
		43	21				15,7±8,46	10,25±6,63		33,9	19,8		18,9	4,73
Zhang China	2016	31		118±36		117±38	4,5±1,3	21±12					5	
		33		266±70		148±47	6±1,2	22±6					7	
Luo Chengdu-China	2015	53	16	265±57		222±51	13±4							21
		53	19	332±73		175±35	17±6							18
Beppu Kumamoto-Japan	2015	52	4	923±735	2	350,5±88,1	18,5±8,9			41,2	33		16,7	8,37
		52	11	1092±749	2	381,8±104	30,75±17,5			42,5	38,1		19,2	9,6
Cheung Hong-Kong-China	2015	24	4	178±126	0	220±103	5,8±2,3		24	21	17	23	17	12
		29	2	722±530	2	216±64	9,8±4,7		27	24	23	20	18	18
Yamashita Fukuoka-Japan	2014	63	6	456±742	4	299,5±128	10,3±4,4	7,4±8,7					43	21
		99	26	437±321	2	287±83	16,2±13,4	5,8±6,9					69	41
Memeo Creteil-France	2014	45	9	475±340,6	0	171,3±72	20,8±15,7	17,5±11	40		27	36		9
		45	20	600±454	0	202,5±61	14,5±7,7	17,5±13,1	28		20	27		10
Kim Seoul-Korea	2014	29	4	484±820	1	210,5±82	7,7±2,9	11,1±6,8	29	29	27	24	18	16
		29	11	261±301	0	203,5±51,1	13,4±7,3	10±7,5	28	27	25	23	18	12

Table 15. (Cont.) Baseline descriptive results from all eligible studies.

MINOR-ONLY														
Author Country	**Year**	**N lap N open**	**Complications**	**Blood loss**	**Transfusions**	**Operative time**	**Hospital stay**	**Mean resection margin**	**1y survival**	**3y survival**	**5y survival**	**1y DFS**	**3y DFS**	**5y DFS**
Kanazawa Osaka-Japan	2013	28	3	269±223,7	0	260±111	12,8±4,8	7±4,5						
		28	20	560±266	4	235,8±70	23,8±10,2	5,25±3,7						
Cheung Hong Kong-China	2013	32	2	465±329	0	246±91,9	6,5±3,4	12,3±7,3	31	28	25	28	23	17
		64	12	838±567	3	295,3±136	15±8,1	12,8±7,5	61	47	36	41	32	28
Kobayashi Osaka-Japan	2013	24	0	350±303	0	206,5±91,4	11,3±2,3		24	24		22	12	
		27	0	788±538	0	230±77,6	18,3±6,8		27	27		26	17	
Truant Lille-France	2011	36	9	452,2±442	1	193,4±104	6,5±2,7	9,5±2,8			25			13
		53	19	447,2±450	2	215,8±88,7	9,5±4,8	8,6±1,7			24			18
Belli Naples-Italy	2007	23	5	260±127	0	148±29,7	8,2±2,6		22	15		18	12	
		23	17	377±114	4	125±17,5	12±3,9							
Kaneko Tokyo-Japan	2005	30	3	350±210		182±38	14,9±7,1				18			9
		28	5	505±185		210±40	21,6±8,8				17			8
Laurent Creteil-France	2003	13	4	620±130	1	267±79	15,3±8,6	9±2,5		12			6	
		14	13	720±240	4	182±57	17,3±19	8,8±1,2		8			6	
Shimada Fukuoka-Japan	2001	17	1	546±696,8	1	323±175	12±5	8±7						
		38	4	808±482	2	271±79,4	22±8	7±6						

Table 15. (Cont.) Baseline descriptive results from all eligible studies.

MAJOR-ONLY														
Author Country	**Year**	**N lap N open**	**Complications**	**Blood loss**	**Transfusions**	**Operative time**	**Hospital stay**	**Mean resection margin**	**1y survival**	**3y survival**	**5y survival**	**1y DFS**	**3y DFS**	**5y DFS**
Zang China	2016	20	0	180±20,5	0	143±35,6	7±1	21,25±3,8	20			20		
		25	10	350±45,3	0	137±29,8	12±2	22±3,7	25			25		
Komatsu France	2016	38	12	280±205,9	2	377,5±98,1	17,3±11,2			28			19	
		38	23	245±182,6	2	308,8±50,3	19,5±11,2			26			11	
Cho Seoul-Korea	2015	24	2			567,4±212	10,6±4,8	30±58			19			10
		19	4			316,1±63	11,1±3,2	70±50			15			10
SOLITARY TUMORS														
Luo Chengdu-China	2015	53	16	265±57,4		222,5±50,7	13±4							
		53	19	332,5±72,9		175±35,3	16,8±6							
Ahn Daegu-Korea	2014	51	3	350±432,5	3	210,7±131	8,2±4,6	17±17			40,9			34,6
		51	5	355,2±321	5	202±50,7	12,3±8,6	13±8			43,7			28
Kim Seoul-Korea	2014	70	5		17	215,5±122	12±23	10±13,7		46	42		41	36
		76	11		31	282±80,3	17±16	8±8,2		50	44		48	41
Ai Putian-China	2013	97	9	460±426	4	245±105	8,2±3,6	15,3±5,9	91	83		90	64	
		178	53	454±365	5	225±112	13,5±3,8	13,6±6,2	169	157		164	119	

Table 15. (Cont.) Baseline descriptive results from all eligible studies.

SOLITARY TUMORS														
Author Country	**Year**	**N lap N open**	**Complications**	**Blood loss**	**Transfusions**	**Operative time**	**Hospital stay**	**Mean resection margin**	**1y survival**	**3y survival**	**5y survival**	**1y DFS**	**3y DFS**	**5y DFS**
Kim Gwangiu-Korea	2011	26	1		5	210±115	11,1±5					22		
		29	7		7	238±93,7	16±11					24		
Nguyen Pittsburgh-USA	2011	17	6	101		235	4,1	11,2	14	12		12	11	
		20	5	164		247	5,7	6,9	17	15		12	9	
Tranchart Paris-France	2010	42	5	364±435	4	233±92,7	6,7±5,9	10,4±8	39	31	25	34	26	19
		42	12	723±559	7	222±46,3	9,6±3,4	10,6±9	34	30	20	30	23	16
Lai Chai Wan-Hong Kong	2009	25	4			146,3±34	7,3±1,8			15			13	
		33	5			110±16,8	15±7,7							
Kaneko Tokyo-Japan	2005	30	3	350±210		182±38	14,9±7,1				18			9
		28	5	505±185		210±40	21,6±8,8				17			8
Laurent Creteli-France	2003	13	4	620±130	1	267±79	15,3±8,6	9±2,5		11,6			5,7	
		14	13	720±240	4	182±57	17,3±18,9	8,8±1,3		7,7			6,4	
Shimada Fukuoka-Japan	2001	17	1	546±697	1	323±174,6	12±5	8±7						
		38	4	808±481,5	2	271±79,4	22±8	7±6						

Table 15. (Cont.) Baseline descriptive results from all eligible studies.

COMBINED														
Author Country	**Year**	**N lap N open**	**Complications**	**Blood loss**	**Transfusions**	**Operative time**	**Hospital stay**	**Mean resection margin**	**1y survival**	**3y survival**	**5y survival**	**1y DFS**	**3y DFS**	**5y DFS**
Takahara Japan	2015	387	26	219,3±297	28	294±158	13,3±6,7		370	334	297	324	226	158
		387	50	415±375,7	38	271±130	17,3±10,4		370	325	274	308	195	152
Han Seoul-Korea	2015	88	11	3675±2784	18	370±163	14±6,5	22,5±13,7	81	77	67	61	46	39
		88	18	3025±2231	23	400±169	42,3±28,7	30±21,2	82	77	64	66	44	36
Lee Toronto-Canada	2015	43	10	1775±1487		241±103	16±11	21,75±13,5						
		86	34	1225±715,8		207±3±60	24±15	26±15,5						

5.4. Export of results to the EGMLLS

The evaluation of a body of evidence should be completed before deciding guidelines recommendations. The quality of available evidence is the cornerstone over which conclusions are held.

The Southampton Guidelines derived from the above mentioned methodology and thus, are based on published evidence and expert opinions (52). After carrying out the literature search described above and evaluating the manuscripts to obtain the highest level of evidence, a complex process for the development of a former guidelines document starts. In this case a guideline for the surgical approach in liver resection (HCC).

In the first stage for this development, after the selection of experts, the steering committee identifies relevant topics to be addressed according to the purpose of the guidelines. In the last Southampton consensus two clinical questions were proposed for HCC:

- CQ1: Are LLR indicated for the management of HCC? Short-term outcomes/Oncologic and Long-term outcomes
- CQ2: What is the role of LLR in cirrhotic patients? Short term outcomes/Oncologic outcomes/Special advantages/difficulties for cirrhotic patients/Technical aspects for liver resections in cirrhotics.

The second stage consists of formulating recommendations and developing an agreement. The expert panel formulated recommendations in response to the CQs by the SIGN Methodology. The process starts with a critical appraisal of the literature, including the assessment of the study quality and the evidence levels available for each topic. After this, recommendations are produced.

For an adequate appraisal of the quality of evidence to the clinical question it is mandatory to perform several questions: How reliable are the studies in the body of evidence?/ Are the studies consistent in their findings?/Are the studies relevant to our target population?/ How sure are we that estimates of the size of effect are reliable?/ Are we sure of all the relevant evidence?. These questions must be answered, therefore exposing the level of evidence available.

5.4.1. Quality of evidence CQ1

For the ***clinical question number 1: Are LLR indicated for the management of HCC? Short-term outcomes/Oncologic and Long-term outcomes?***, the quality of evidence obtained based on SIGN methodology is:

To the question: ***How reliable are the studies in the body of evidence?***

There are three meta-analyses (17 studies/7 studies/4 studies), 53 comparative studies and 24 series studies (non-comparatives) that compared laparoscopic vs open approach in HCC patients. These studies follow the SIGN minimum rules for evidence-based analysis. The statistics methodology and bias assessment were good in general; however, the common problem of all of these studies is that all collected manuscripts collected are observational, retrospective and non-randomized.

The number of patients and the sample size of each study were not very high (from 20 to 200). Eight (61) (111) (62) (60) (102) (59) (58) (107) of the 53 comparative studies used Propensity score matching methods to improve the level of evidence and avoid biases that might occur during the sample selection process. ***Evidence level 1+***.

Laparoscopic LLS and minor LLR for HCC patients are now considered standard approaches (61) (103), especially for tumors located in the anterolateral segments. These patients show lower transfusion rate, lower risk of bleeding, shorter hospital stay and fewer complications. ***Evidence level 1++***.

Recent studies question whether there are benefits of using laparoscopy in complex resections such as posterosuperior segments (high Iwate score). Xiao (79) with a case-control study with over 127 patients without PSM concluded that LR for HCC patients in these segments might offer the same oncologic outcomes as an open approach. LR is associated with several advantages as lower

blood loss, fewer complications and shorter hospital stay. ***Evidence level 2+*.**

Regarding major hepatectomy for HCC patients, there are several comparative studies. Komatsu (80) does a comparative study to identify the benefits of the laparoscopic approach in major resections. The sample size is very small. This was an intention-to-treat analysis; for this reason, the 12 converted cases in the laparoscopic group were analysed as laparoscopic cases, resulting in not very reliable conclusions.

Ai et al. (108) did an interesting study about patients who underwent major resection for HCC greater than 5 cm. The majority of the patients underwent major hepatectomy or with high Iwate score. Over 275 resection, they concluded that there were no significant differences in the mean operative time (p=0.469), mean estimated intraoperative blood loss (p=0.913), or blood transfusion (p=0.480) between the laparoscopic and open group. There was a lower rate of postoperative complications in these patients, being the hospital stay shorter than in the open group (p=0.028).

The principal selection bias in this study was that patients with previous surgery were excluded from the laparoscopic group and they did not do a subgroup analysis over major/minor resection. Most of the studies showed that the short-term outcomes were superior compared to the open approach (fewer complications) and that technical feasibility has been proved in expert centres. ***Evidence level 2-***.

Regarding complex resections with high Iwate score (as posterosuperior segments), there are a few numbers of manuscripts. The most recent is from Xiang et al. (112) where over more than fifty patients had been diagnosed with HCC in posterosuperior segments, and a comparative study versus anterolateral segments resections was performed.

Authors concluded that the operation time is longer in these patients (217.5 ± 63.7 vs 176.8 ± 48.4 min, p = 0.000), because of the process required the full mobilization of the liver and more time to expose the lesion.

The number and duration of Pringle's cycles are higher and thus, enzyme peak is higher in these patients.

Xiao et al (79) did another interesting study in the same year, comparing open versus laparoscopic approach in posterosuperior segments. They concluded that intraoperative blood loss was significantly lower and postoperative hospital stay significantly shorter in the LLR.

The overall complication rate was significantly lower in the laparoscopic group (p=0.021). Liver resection in HCC patients in the posterosuperior segments might offer the same oncologic outcomes as with conventional procedures while being associated with such advantages as lower blood loss, fewer postoperative complications and shorter hospital stay. ***Evidence level 2-***.

Regarding short-term results, there are several comparative studies (some of these with PSM) and three meta-analyses. Leong (113) and Chen (68) concluded that operative time seems to be similar between both groups (p=0.2) (due to the improvement with the progression of the learning curve). Blood loss (p=0.03) and need of transfusions (p=0.004) are lower in patients undergoing LLR than OLR.

Postoperative morbidity is significantly lower (p<0.0001) in LLR group (fewer ascites, less infection, less chest complication, less pleural effusion and less abdominal wall complications), similar postoperative mortality (p=0.48) and shorter hospital stay (p=0.0002). ***Evidence level 1+***.

Regarding long-term and oncological results, tumor margin was not different in comparative studies. Twaij et al. (63) showed wider resections margins in laparoscopic approach; this might be explained because the tumor size in the open group is usually bigger and closer to vessels and hepatic pedicles. Overall survival and disease-free survival rates are similar in both groups in comparative and review studies.

In different studies, the disease-free survival rate seems to be better in LLR group than in OLR. This might be because patients in LLR group may

undergo a selection bias and have smaller tumor size. ***Evidence level 2+***.

To the question: ***Are the studies consistent in their conclusions?***

It is possible to conclude that there are no inconsistent studies in the laparoscopic approach for the treatment of HCC patients. All studies published at the moment concluded the same results.: the fair benefits of this approach in these patients. The lowest evidence could be found on the disease-free survival rate of these patients.

This is because in most of the studies, the follow-up period remains short. Furthermore, the main limitation is that all comparative studies included are non-randomized controlled studies with a retrospective matching. Selection of patients in both groups tends to be heterogeneous. However, it is unknown whether patients in the open group tend to have greater size tumour and closer to main vessels. Matching and PSM analysis try to avoid these selection biases.

To the question: ***Are the studies relevant to our target population?***

It is possible to conclude that most of the results from our studies might be exportable to other populations. There are two main comparing groups (open and laparoscopic) with equivalent characteristics as tumor size, ASA score and number of segments resected. Most of the studies have similar aims (short and long-term outcomes/oncologic outcomes and survival and disease-free survival rates).

Results are depicted using same measurement units (blood loss, transfusion rate, operative time, tumor size, Pringle's cycle) and use a recognized definition of the complications, including most commonly used scales (Dindo Clavien). A high number of studies use several methods to avoid selection bias as matchings and propensity score matching and an adequate technical description of each technique is performed in most of the studies.

To the question: ***Are there concerns about publication bias?***

Publication bias is a type of bias that occurs in published academic research. It happens when the outcome of an experiment or a research study influences the decision of whether to publish or otherwise distribute it. Multiple factors contribute to this publication bias and may be difficult to be controlled. In this case, a strict literature search without language restrictions on MEDLINE, EMBASE, and the Cochrane Library has been performed.

Eligible studies were identified using the following index words: hepatocellular carcinoma or HCC or hepatic tumour; open surgery or open hepatectomy or open liver resection; laparoscopic surgery or laparoscopic hepatectomy or laparoscopic liver resection. The studies included should compare the two types of approach, should report data on short-/longterm outcomes and intraoperative outcomes. In this literature review, publication bias has not been reported.

5.4.2. Quality of evidence CQ2

For the ***clinical question number 2: What is the role of LLR in cirrhotic patients? Short term outcomes / Oncologic outcomes / Special advantages / difficulties for cirrhotic patients / Technical aspects for liver resections in cirrhotics***, the quality of evidence obtained based on SIGN methodology is:

To the question: ***How reliable are the studies in the body of evidence?***

There are two systematic reviews and eight comparative studies on patients diagnosed with HCC undergoing laparoscopic surgery compared with open surgery. Liver resection in cirrhotic patients was reported to have higher morbidity rates compared to non-cirrhotic patients. With the advancement of laparoscopic surgery, this approach could be beneficial in cirrhotic patients and prevent existing complications after open surgery.

Regarding short-term outcomes, most of the studies show a superiority of the laparoscopic approach versus open in HCC in cirrhotic patients. In general, for cirrhotic HCC patients, more postoperative adverse events might happen,

including infections, pleural effusion, or liver failure. In the meta-analyses by Chen (68) tumor margin is significantly wider in the laparoscopic group than in the open group (p=0.002). However, operative time seems to be similar in both groups. In laparoscopic groups,less transfusion are need (p=0.004) and less blood loss is reported (p=0.03).

Postoperative complications are significantly lower in the laparoscopic group (P<0.0001). The kind of approach does not seem to have an impact on postoperative mortality (p=0.48) (68). ***Evidence level 1+***.

Regarding long-term and oncological outcomes, no significant survival rate benefit was shown between both groups. Belli et al (67) showed a trend towards better survival benefit in laparoscopic approach in HCC patients with liver cirrhosis.

The authors reported a wider resection margin (p<0.0001) and a theoretical better visualization of micro-invasive satellite vascular areas. ***Evidence level 2++***.

In recent studies, Shehta (114) and Han (60), also reported interesting results. In laparoscopic resection performed Child-Pugh-C patients. Although all patients underwent minor resections, recovery after surgery without significant morbidities was reported. ***Evidence level 2+***.

Regarding technical concerns, one of the major drawbacks of LLR in cirrhotic patients is the risk of massive bleeding. Cirrhotic patients are at high risk of bleeding mainly due to primary hemostasis dysfunction. The reason for conversion in most manuscripts is bleeding from parenchymal transection.

Twaij et al. (63) reported significantly lower blood loss in the laparoscopic group compared to the open groups (p<0.001). This finding was explained thanks to high-definition laparoscopic devices which allow magnification, enabling surgeons to obtain a decent view for performing proper haemostasis.

A secondary point is the better access and exposure during a salvage transplant after a primary resection for an HCC. In this sense, laparoscopic approach versus open may reduce adhesions and bleeding in a further transplant.

Some manuscripts have reported improved results in the hepatectomy phase of the transplant and a smaller cold ischemia time in these patients (114). ***Evidence level 2++***.

To the question: ***Are the studies consistent in their conclusions?***

There are no inconsistent studies in the minimally invasive approach for HCC in liver cirrhotic patients. The lowest evidence was obtained due to the impossibility to reach an accurate conclusion regarding the benefits and risks of laparoscopic resection in the absence of RCTs.

To the question: ***Are the studies relevant to our target population?***

Most of the results from our studies might be exportable to other populations. However, some difficulties may be considered. Few papers have evaluated laparoscopic resection for HCC in cirrhotic patients.

The patients in the open group have bigger tumour size and underwent more complex resections compared to laparoscopic approach group (important selection bias of these studies).

To the question: ***Are there concerns about publication bias?***

Eligible studies were identified using the following index words: cirrhosis or cirrhotic; hepatocellular carcinoma or HCC or hepatic tumour; open surgery or open hepatectomy or open liver resection; laparoscopic surgery or laparoscopic hepatectomy or laparoscopic liver resection.

The studies included should compare the two types of approach, should report data on short/long-term outcomes and intraoperative outcomes.

In this literature review, publication bias has not been reported and do not appear from the studies considered.

5.4.3. Evidence to recommendations and making recommendations

One of the factors that seem to influence a practitioner's decision to implement a recommendation is the degree of confidence that they have in it; that is, how certain they are that following the recommendation will produce the expected improvement in the outcome for their patients.

Not only does this certainty relate to the degree of confidence in the size of the effect of an intervention in relation to specific important outcomes, but it also encompasses other issues such as patient preferences and the availability of resources to support the introduction of a new intervention.

For this reason, the guideline development group has to consider both the overall quality of the supporting evidence and the other factors that might influence the strength of the recommendation.

The guideline development group should focus on outcome, impact, number of studies and quality/certainty of the body of evidence. Fundamental to making any recommendation is the need to have a clear understanding of how substantial the expected benefits of an intervention are likely to be in practice.

The guideline development group also needs to consider how substantial the downsides are. Balancing all the issues described is complex and presents a challenge to any guideline group. The outcome of the decision-making process is to produce a recommendation that is rated as either strong or conditional.

High-quality evidence from well-conducted studies should lead to a strong recommendation but relating the trial populations to the target population of a guideline and taking into account issues of cost and patient acceptability might lead to a recommendation that is much weaker than first thought. Likewise, there will be circumstances where the evidence is flawed but there are few or no downsides to treatment and the clinical importance of the topic is such that a strong recommendation is justifiable.

5.4.4. Statements and recommendations to CQ1 (Appendix 5)

Laparoscopic liver resection for HCC offers better postoperative outcomes in selected patients when compared with open resections in terms of a decreased morbidity and hospital stay without compromising oncologic outcomes. Evidence level 1-, Form of recommendation: Strong.

To the question whether LLR is indicated for the management of HCC, several meta-analysis and large propensity score-matched studies of open versus laparoscopic liver resection for HCC have strongly suggested that LLR for HCC is associated with reduced blood loss, transfusión rate, postoperative ascites, and liver failure and hospital stay with comparable operation time, disease-free margin, and recurrence rates (115) (62). This has been confirmed for major resections in a recent series (116).

For minor resections, a laparoscopic approach was found to be the only independent factor to reduce the complication rate in resections for HCC (61).

Leong (113) performed a comparative study over 152 patients (LLR vs OLR) and concluded that the duration of operation in the LLR group was significantly shorter. Similarly, intraoperative blood loss, need for transfusions and hospital stay were also lower. There was no difference in the overall complications rate or specific complications. Laparoscopic approach was equal in terms of tumor recurrence and did not impact the oncologic outcomes (overall survival and disease-free survival rates).

Moreover, a significant increase in disease-free survival rates in the LLR group [52.5% DFS at 5 years for LLR group Vs 38.2% for OLR p=0.035] (maybe due to the higher incidence of microvascular invasion found in the open group) was reported. The authors performed a parallel meta-analysis of 17 studies with favourable results to minimally invasive approach in terms of hospital

stay and postoperative complications. No significant differences were observed between LLR and OLR in regards to post-operative mortality (P=0.07).

Chen (68) performed a systematic review and meta-analysis on 7 comparative studies. They concluded that the tumor margin was significantly wider in LLR than in OLR (p=0.002); however, curative resection in LLR was not significantly better than in OLR patients (p=0.26).

Operative time was similar between both groups. Blood loss (p=0.03) and need of transfusions (p=0.004) were lower in patients undergoing LLR compared to OLR.

Postoperative hospital stay and morbidity were significantly lower (fewer ascites, less infection, less chest complication, less pleural effusion and less abdominal wall complications).

Regarding oncological outcomes, patients in the LLR group have higher 5 years survival rate than OLR (p=0.04); however, the disease-free survival rate is similar in both groups.

Sposito et al. (61) recently reported a propensity score matching analysis of two comparable groups of 43 LLR and OLR patients. Complications rate and hospital stay were significantly lower in the LLR group.

They performed a multivariable logistic regression analysis in which the only independent factor that reduced the risk of postoperative complications was the use of laparoscopy (odds ratio 0,12 [0.03-0.55] CI 95). Long-term outcomes were not different between groups.

The laparoscopic approach seems to be superior to the open approach in terms of hospital stay, transfusion rate, operative time, blood loss and postoperative complications without compromising oncologic outcomes.

However, it should be kept in mind that they are usually based on studies in which patients might have had some kind of selection bias (size and location of the tumour, superficial or peripheral locations).

For HCC, indications and type of resection should not differ between laparoscopic and open approaches. For HCC located in the postero-superior part of the liver (i.e. segments 1, 4a, 7 and 8) laparoscopic resection is technically demanding, not well standardized yet and should only be performed in experienced centres. Evidence level: 2-. Form of recommendation: Conditional.

Procedures on posterosuperior (PS) segments of the liver are more challenging than those on anterolateral (AL) areas and should be reserved for experienced surgeons at major laparoscopic centres. Advances on laparoscopic techniques and surgical equipment have made LLR of lesions located in the PS segments safe and feasible (117). LLR for HCC in the PS segments is technically demanding, and the key to the success of this procedure lies in surgical field exposure, bleeding control and safe margin determination. The studies to answer this question are scarce.

The most recent study is from Xiang (112) with more than fifty patients with the diagnosis of HCC in PS segments; and where a comparative study versus resections on AL segments is performed. They concluded that operation time is longer in PS resections (217.5 ± 63.7 vs 176.8 ± 48.4 min, P=0.001), because they required the full mobilization of the liver and more time to expose the lesion.

The number and duration of Pringle's cycles is greater, and thus, enzyme peak is higher. As Xiao states (79) the resection of HCC located in PS segments is one of the most complex procedures. Xiao (79) showed significant advantages in short-term outcomes for laparoscopic approach, shorter hospital stay (p=0.000) and less blood loss (p=0.001). The overall complication rate was significantly lower in the laparoscopic group (p=0.021).

Liver resection in patients with an HCC located in the PS segments might benefit from laparoscopic approach as it may be associated with lower blood loss, fewer postoperative complications and shorter hospital stay.

Current studies on this subject are no meta-analysis nor randomized studies, and subsequently, conclusions obtained from the few number of comparative studies and case series are limited.

As for other indications, intermittent clamping, selectively applied in patients with HCC, might help to decrease blood loss without detrimental effects on liver function. Evidence level: 4. Form of recommendation: Strong.

The conclusions regarding this clinical question are based on expert opinions due to their experience and their observation in the clinical practice. Growing evidence supports that excessive blood loss and the need for blood transfusions are predictors of poor outcome in liver resections for both cirrhotic and non-cirrhotic patients.

Dua (118) performed a comparative study about the use of intermittent clamping (IC) for parenchymal transection in laparoscopic liver resections. This manuscript concluded that there were no postoperative differences in the peak of AST and ALT (p=0.15 and p=0.14) and neither in serum bilirubin or INR (p=0.69 and p=0.62) between IC and no IC groups.

This study has a high selection bias because patients in which IC was performed had higher rates of major resections and longer operative times. In the last Consensus Conference held in Morioka in 2014 (51) the conclusions about essentials in bleeding control were centrally based on CO_2 pneumoperitoneum.

Authors concluded that, in case of severe bleeding, increasing the pneumoperitoneum pressure and decreasing the airway pressure by a brief pause in the artificial ventilation are manoeuvres that can be used to decrease back-bleeding.

When used together with low central venous pressure and high CO_2 pneumoperitoneum pressure, IC is especially effective in preventing blood loss. To address ischemia-reperfusion injury, which is a major concern in this technique, IC and ischemic preconditioning have been proposed as modifications of the original (119).

The conclusions arising from expert's opinion were that IC can be used if necessary. Blood loss can be reduced by careful application of ultrasonic dissectors. Careful administration of intravenous fluid and tight maintenance of low central venous pressure also contribute to minimal oozing during liver transection. In laparoscopic hepatectomy, raising of intra-abdominal pressure also leads to a relative reduction in venous pressure during liver transection. Randomized trials and comparative studies are encouraged in order to scientifically prove the benefits of IC in patients undergoing laparoscopic liver resections.

In experienced hands, laparoscopic major resections for HCC are an appropriate option, like for open surgery, in highly selected patients. Evidence level: 2++. Form of recommendation: Strong.

Few manuscripts compare major LLR versus OLR. Zhang (81) compared 20 left hemi-hepatectomies and concluded that LLR offers less blood loss (p<0.05), less hospital stay (p<0.05) and less postoperative morbidity rate with a mean operative time similar in both groups (143 min vs 137 min). The oncologic outcomes were similar in both groups.

Komatsu (80) performed a non-randomized comparative study including 76 patients (38:38) in an intention-to-treat basis and demonstrated the technical feasibility and superior short-term outcomes with equal oncological results with a minimally invasive approach. The overall complication rates were significantly higher in the open group than in the laparoscopic group (65% vs 32%, respectively; p=0.011).

Moreover, the laparoscopic approach showed a trend toward shorter, although not statistically significant, length of postoperative hospital stay (p=0.079). Cho (83) analysed the results of 24 major LLR vs 19 OLR, obtaining similar results. The mean operative time was longer in the laparoscopic group. There was no difference in the mean resection margin and the rate of postoperative complications. The duration of hospital stay in LLR group was shorter but not statistically different.

5.4.5. Statements and recommendations to CQ2 (Appendix 6)

In patients with cirrhosis, the risk of postoperative ascites and decompensation might be lower than expected with open resections. Evidence level: 1+. Form of recommendation: Strong

To the question of what is the role of LLR in cirrhotic patients, no differences in operative time, blood loss, intraoperative complications, hospital stay and morbidity were found in LLR for cirrhotics compared with noncirrhotics (114).

The laparoscopic approach appears to reduce the incidence of postoperative ascites, liver failure (81), and morbidity assessed in terms of "comprehensive complication index", with no difference in overall or disease-free survival rates at 2 years (72). The evidence for both LLR in patients with significant portal hypertension, ascites, and Child-Pugh B cirrhosis is limited to single studies, (120) (121), and therefore, the guidelines recommend caution with these patient cohorts.

Numerous studies have reported the potential benefits of laparoscopic liver resection in cirrhotic patients. There are two main groups of studies. The first ones compared the laparoscopic approach in cirrhotic livers versus non-cirrhotic patients (114) (122). The second group compared laparoscopic versus open approach in cirrhotic liver patients (68) (71) (63) (69) (70) (64) (65) (67).

Chen (68) performed the most recent meta-analysis, excluding patients with severe cirrhosis. The rest of the studies excluded patients with Child-Pugh Score of C, except Truant (66) who also excluded Child B patients and those with portal vein thrombosis.

Shehta (114) performed a well-designed retrospective case-control study analysing 232 patients, 141 of which had biopsy-proven cirrhosis. There were no statistically significant differences between both groups regarding operation time, blood loss, transfusion requirements, intraoperative complications, hospital stay and postoperative complications. Postoperative ascites was not specifically analyzed.

Similarly, although Belli (67) reported a lower complication rate, liver-related ones as ascites or failure were not analyzed. Yamashita (71) compared 63 laparoscopic vs 99 open procedures in cirrhotic patients. Morbidity rates in the laparoscopic group (10%) were significantly lower than in the open group (26%) p=0.0459. The rate of ascites in the laparoscopic group (0%) was significantly lower than in the open group (7%) p=0.0077.

The same happened with hospital stay, which was shorter in the laparoscopic group (p=0.0008). Memeo recently reported their series (69), in which complications in the laparoscopic group (20%) was much lower than for open patients (45%). No differences were detected in the type of postoperative complications, except for postoperative ascites, which was higher in the open group (18 vs 2% p=0.01), as was the development of postoperative liver failure (5 vs 1), although this was not statistically different (p=0.09).

Kanazawa (64) also showed a higher incidence of intractable ascites in the open group (p<0.0001). With a high level of evidence, a meta-analysis performed by Morise (72) reported that a minimally invasive approach was associated with a reduced incidence of postoperative ascites (OR 0.26; 95% CI, 0.14-0.49; p<0.0001) and liver failure (OR 0.24; 95% CI, 0.10-0.56;p=0.001).

It should be remarked that in most of the studies, wedge and minor resections were performed in laparoscopic groups, whilst complex procedures were performed in the open approach. Despite these biases, it seems that, even in cirrhotic patients, the laparoscopic approach decreases the incidence of intractable ascites and liver failure, and thus, consequently reduces the length of the postoperative hospital stay.

The extension of indications into patients with significant portal hypertension (i.e. hepatic venous gradient ≥ 10mmHg) or ascites requires further evaluation. Evidence level: 3. Form of recommendation: Recommendation for research.

Morise (123) concluded that, for cirrhotic patients with liver tumors, pure laparoscopic liver surgery might minimize the destruction of the

collateral blood and lymphatic flow compared with laparotomy. Pure laparoscopic hepatectomy results in minimal postoperative ascites production, which leads to a lower risk of electrolyte imbalance and hypoproteinemia. Accordingly, a lower rate of complications might potentially lead to a reduced incidence of postoperative serious liver failure.

Kanazawa (47) also showed that the laparoscopic liver resections could be considered a safe and feasible procedure even in cirrhotic patients. Cheung (65) performed a high-quality case-control study matching 1:1 over 600 patients with cirrhotic liver (evaluated by Child score and ICG retention).

This study concluded that laparoscopic approach for HCC stage I and II might achieve safety and long-term survival rates equivalent to those achieved by open approach. Randomized or comparative studies in patients with severe cirrhosis and portal hypertension are necessary in order to obtain conclusions regarding this clinical question.

The majority of the studies did not include patients with portal hypertension or Child-Pugh C. The rate of ascites before surgery was not reported in most of the manuscripts. To date, no studies have been performed to find out the possibility of expanding the surgical criteria into patients with portal hypertension or ascites.

Therefore, the indications for surgery in patients with significant portal hypertension or ascites are now equivalent both for the laparoscopic and open procedures. The studies show that a minimally invasive approach for HCC generally yields better short-term outcomes without compromising the long-term outcomes (72).

The role of laparoscopic minor resection for single peripheral or subcapsular HCC in selected Child B patients needs further evaluation. Evidence level: 2-. Form of recommendation: Recommendation for research.

Three manuscripts compared open or laparoscopic approaches vs radiofrequency ablation in subcapsular HCC (111) (124) (125). In general terms, the laparoscopic approach for minor resections in HCC shows several benefits over the open approach (hospital stay, blood loss rate, postoperative pain, need for transfusion, complications rate,…).

According to the Morioka Consensus, overall postoperative complications and length of stay were generally better than for open procedures. No outcomes are worse for the laparoscopic approach (51). Truant (66) performed a case-control study in 36 patients with chronic liver disease and peripheral HCC (laparoscopic group) vs 53 patients who underwent open hepatectomy. Severe complications were more frequent in the open group (p=0.09); meaning that hospitalizations were shorter in the laparoscopic group (p=0.003).

The patients included in this study were patients with Child-A cirrhosis. Patients with Child-Pugh grade B or C were excluded. Studies that include patients with Child-Pugh B stage are very scarce.

Several studies compared laparoscopic versus open approach in patients with cirrhosis in which a few patients with Child-Pugh B were included, but the percentage is still very small. No comparative studies regarding this clinical question have been published to date. Future randomized or comparative studies focusing on patients with Child B stage are needed to answer this question.

5.5. Updated Meta-analysis

All the abovementioned literature search was the basis of the European Guidelines on Laparoscopic Liver Surgery that were published by all the researchers and experts that contributed to their development (52). With all these data, an updated systematic review and meta-analyses was performed by our team. As reported before, all manuscripts were deeply screened and patients were grouped into 5 blocks: Solitary tumors, Child-Pugh A, Minor resections, Major resections and combined resections.

From the initial 361 manuscripts, 28 were included in the meta-analysis. Five of these were specific to patients with CPA cirrhosis (321 cases), eleven focused on solitary tumors (1003 cases)

while sixteen focused on minor (1286 cases) and three in major (164 cases) resections respectively.

All baseline results are depicted in table 15. Each of the subgroups underwent secondary meta-analyses. All the series allocated to each subanalysis were independently assessed for bias in each variable. All the results (funnel plots) were graphically depicted. In this chart, the magnitude of the effect measured against a precision measurement is represented, which is usually the sample size, but which can also be the inverse of the variance or the standard error.

Heterogeneity, reporting bias, and chance might all lead to asymmetry or other shapes in funnel plots. Bellow, the funnel plots for each of the subgroups analyzed are depicted. The heterogeneity analysis is performed on each of the variables represented by I^2 value and its statistical significance.

5.5.1. Solitary tumors

A total of 11 studies were identified, including 562 open resection and 441 LLRS for solitary HCC (Table 15). This group includes patients in whom imaging tests describe a single HCC compatible lesion.

The type of resection performed does not influence, therefore there might be cases in which a major or minor liver resection is carried out. There could be cases in both groups, being the prognosis and clinical environment different.

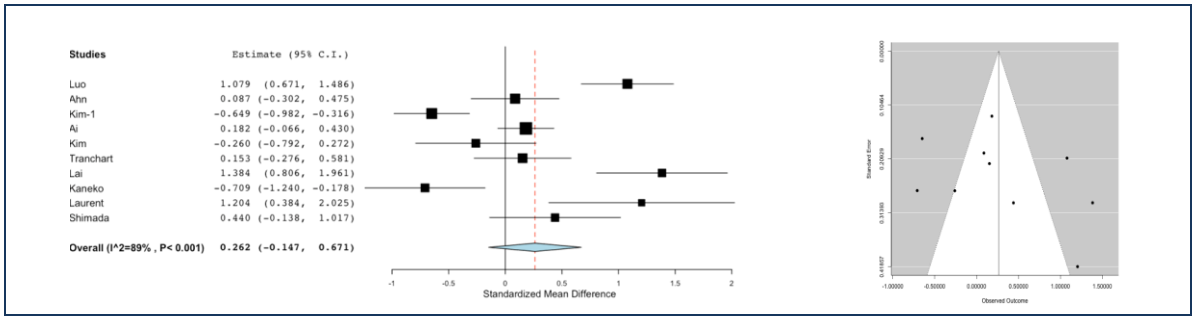


Figure 11. Solitary tumors. Operative time. Heterogeneity p<0.001; I^2 =89%; OR 0.262 [95% CI -0.147-0.671]; p=0.209

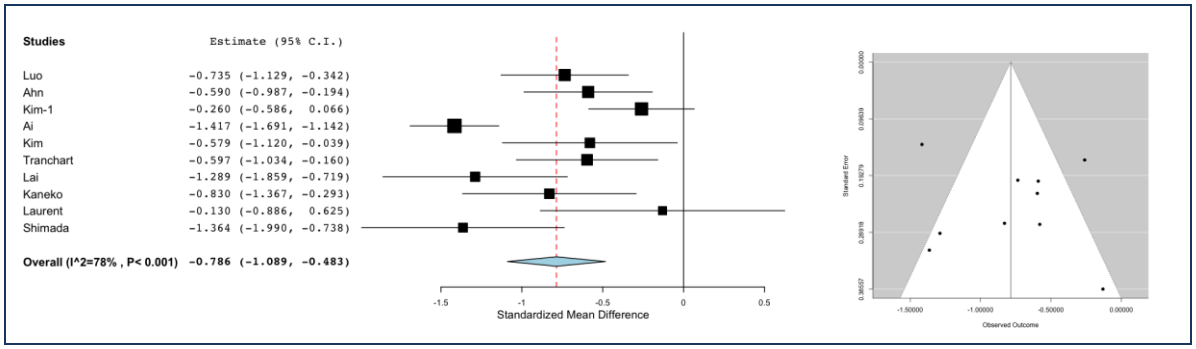


Figure 12. Solitary tumors. Hospital stay. Heterogeneity p≤0.001; I^2 = 78%; SMD -0.786 [95% CI -1.089 to -0.483]; p<0.001

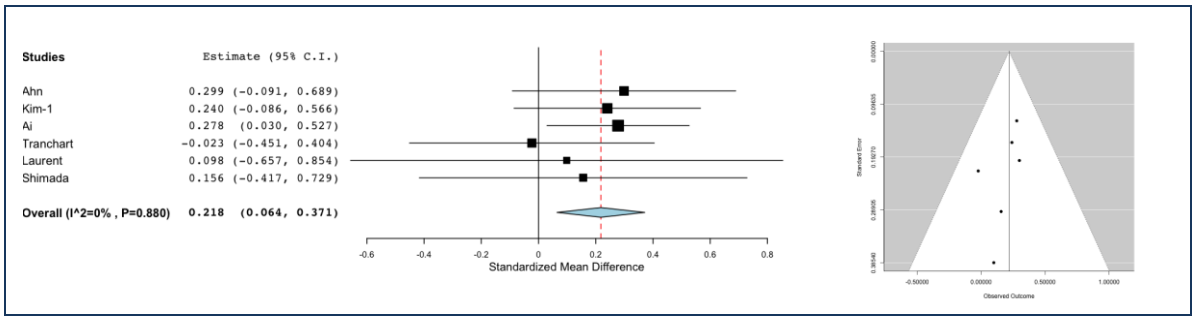


Figure 13. Solitary tumors. Mean resection margin. Heterogeneity p= 0.88; I^2 = 0%; SMD 0.218 [95% CI 0.064–0.371]; p = 0.005

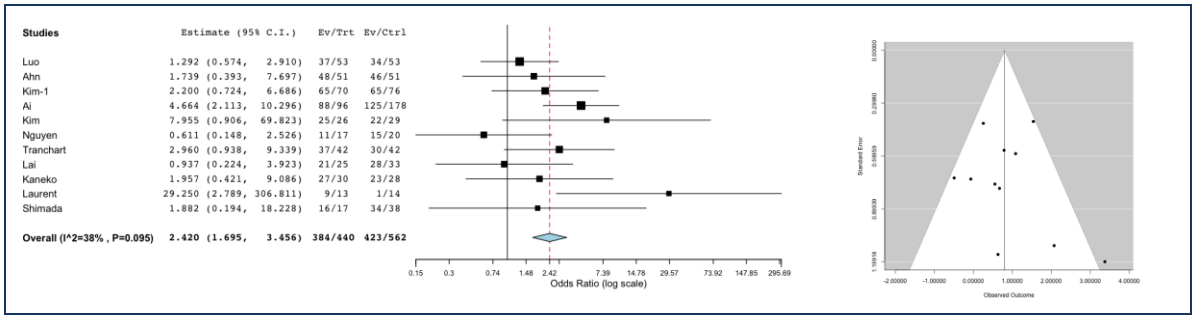


Figure 14. Solitary tumors. Complications. Heterogeneity p= 0.095; I^2 = 38%; OR 2.42 [95% CI 1.695–3.456]; p<0.001

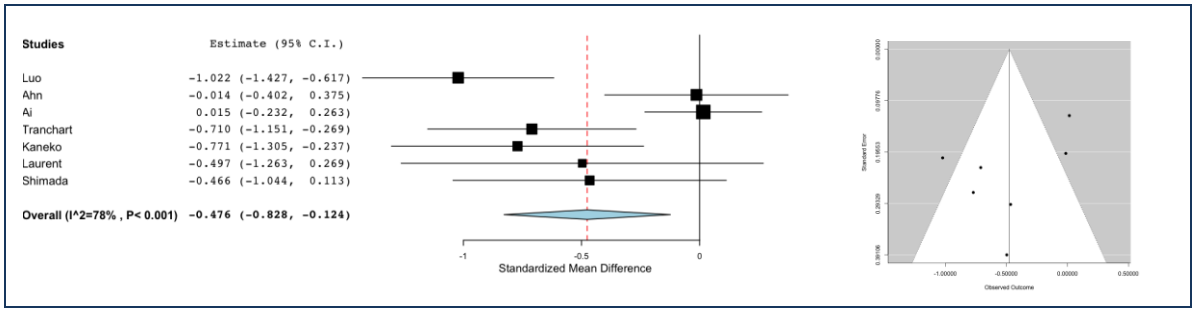


Figure 15. Solitary tumors. Blood loss. Heterogeneity p≤0.001; I^2 = 78%; [SMD] -0.476 [95% CI -0.828 to -0.124]; p<0.008

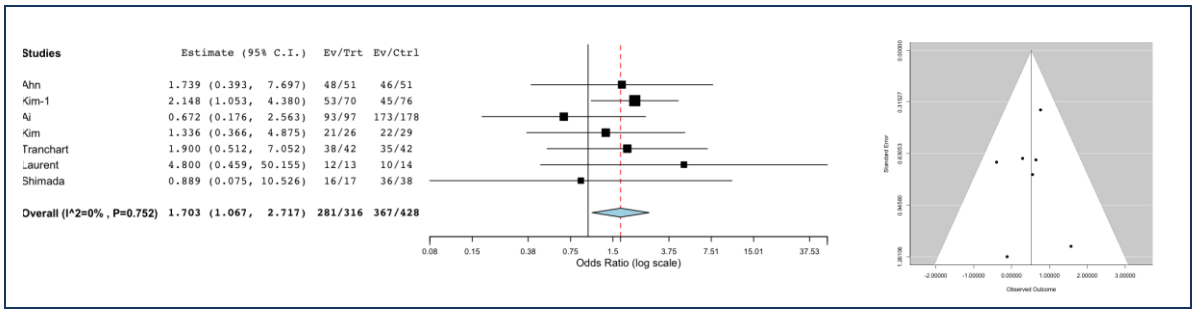


Figure 16. Solitary tumors. Transfusions. Heterogeneity p= 0.75; I^2 = 0%; OR 1.703 [95% CI 1.067–2.717]; p <0.026

Regarding short-term outcomes, it can be seen that the laparoscopic approach provides several benefits in terms of complications rate and others.

Operative times were equal between the groups but all other short-term outcomes, including complication rates (heterogeneity p-value = 0.095; I-squared = 38%; OR 2.42 [95% CI 1.695–3.456]; p<0.001), blood loss (heterogeneity p-value ≤0.001; I-squared = 78%; standardised mean difference [SMD] -0.476 [95% CI -0.828 to -0.124]; p<0.008), transfusions (heterogeneity p-value = 0.75; I-squared = 0%; OR 1.703 [95% CI 1.067–2.717]; p <0.026), hospital stay (heterogeneity p-value ≤0.001; I- squared = 78%; SMD -0.786 [95% CI -1.089 to -0.483]; p<0.001), and resection margins (heterogeneity p-value = 0.88; I-squared = 0%; SMD 0.218 [95% CI 0.064–0.371]; p = 0.005), favored a laparoscopic approach (Figures 11 to 16).

PHLF and Mortality were not significantly different between the groups (Figure 17 and 18) and there were no significant differences in 1-, 3-, and 5-year OS and DFS (Figures 19-24).

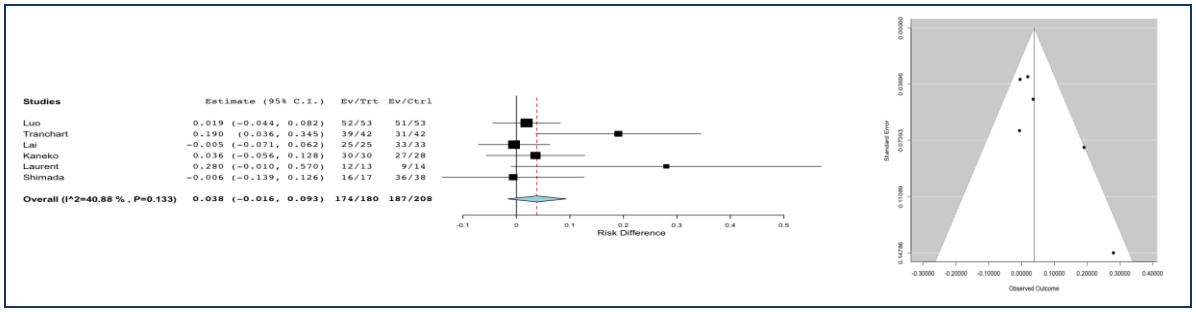


Figure 17. Solitary tumors. Posthepatectomy liver failure. Heterogeneity p= 0.133; I^2 = 40%; OR 0.038 [95% CI -0.016–0.093]; p =0.170

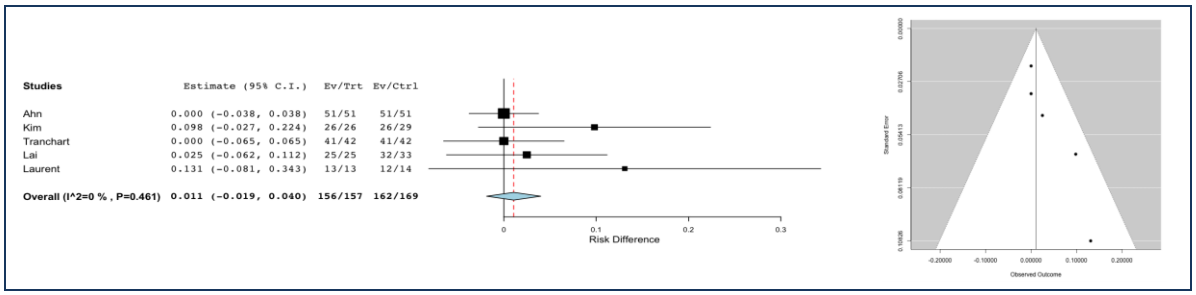


Figure 18. Solitary tumors. Mortality. Heterogeneity p= 0.133; I^2 = 40%; OR 0.038 [95% CI -0.016–0.093]; p =0.170

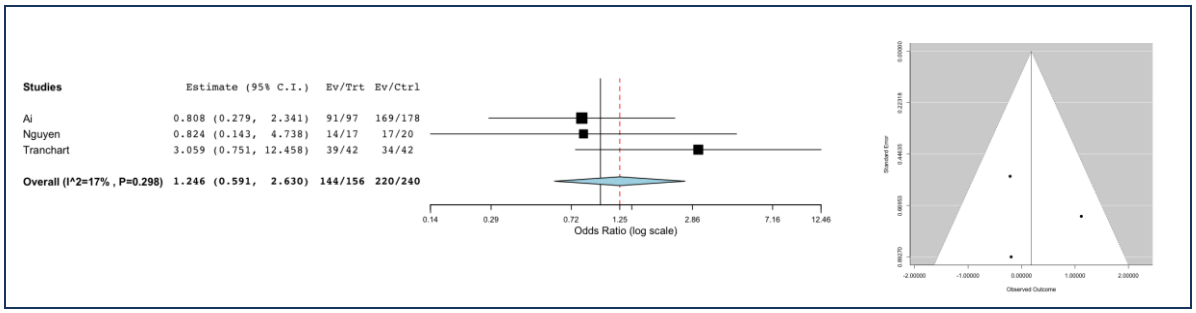


Figure 19. Solitary tumors. 1-y overall Survival. Heterogeneity p= 0.298; I^2 = 17%; OR 1.246 [95% CI 0.591–2.630]; p =0.563

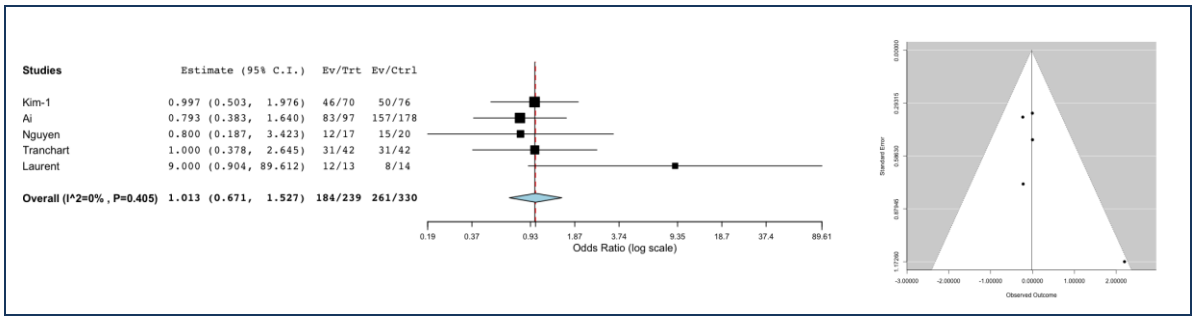


Figure 20. Solitary tumors. 3-y overall Survival. Heterogeneity p= 0.405; I^2 = 0%; OR 1.013 [95% CI 0.671–1.527]; p =0.953

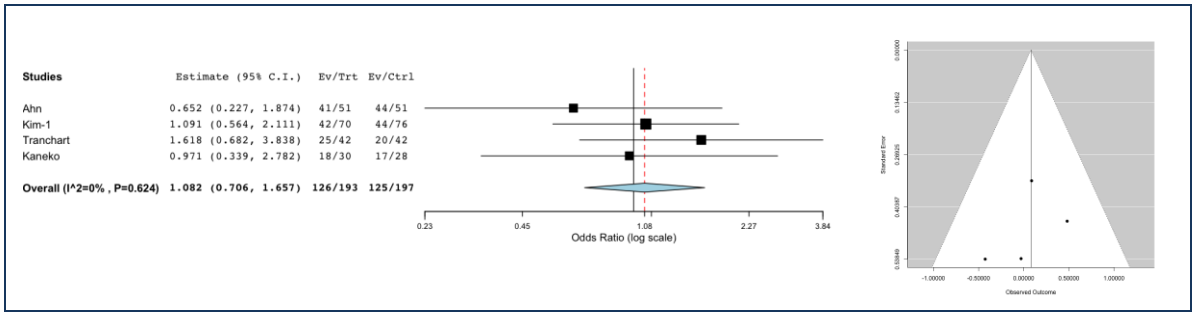


Figure 21. Solitary tumors. 5-y overall Survival. Heterogeneity p= 0.624; I^2 = 0%; OR 1.082 [95% CI 0.706–1.657]; p =0.717

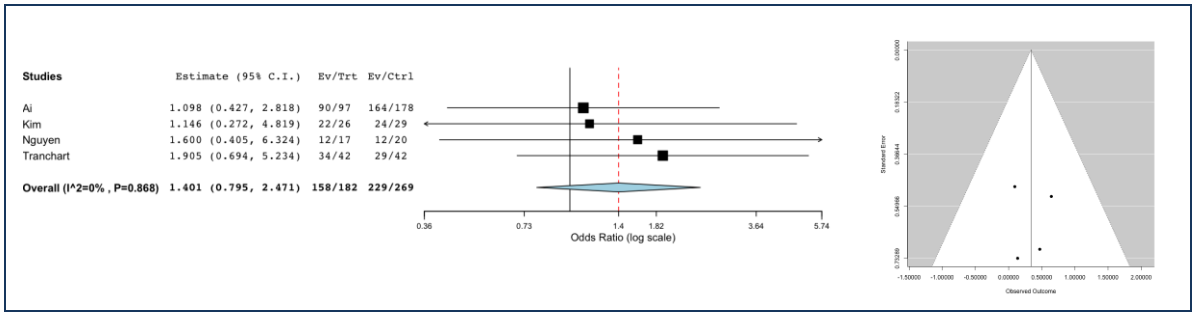


Figure 22. Solitary tumors. 1-year disease-free Survival. Heterogeneity p= 0.868; I^2 = 0%; OR 1.401 [95% CI 0.795–2.471]; p =0.244

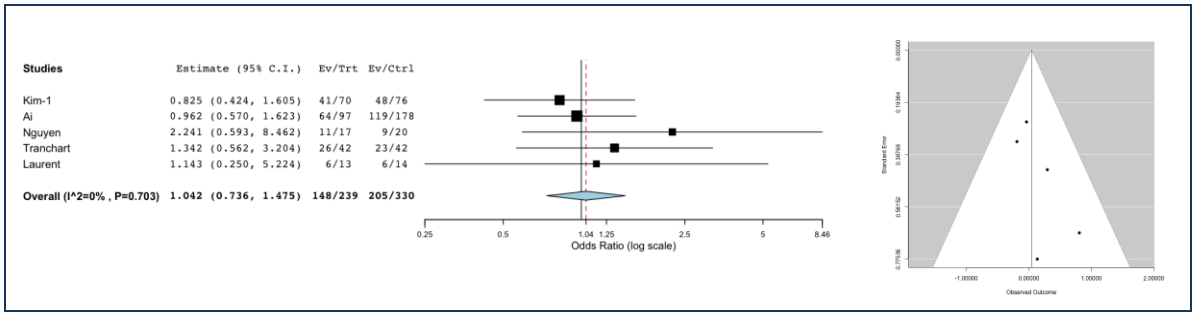


Figure 23. Solitary tumors. 3-y disease-free Survival. Heterogeneity p= 0.703; I^2 = 0%; OR 1.042 [95% CI 0.736–1.475]; p =0.816

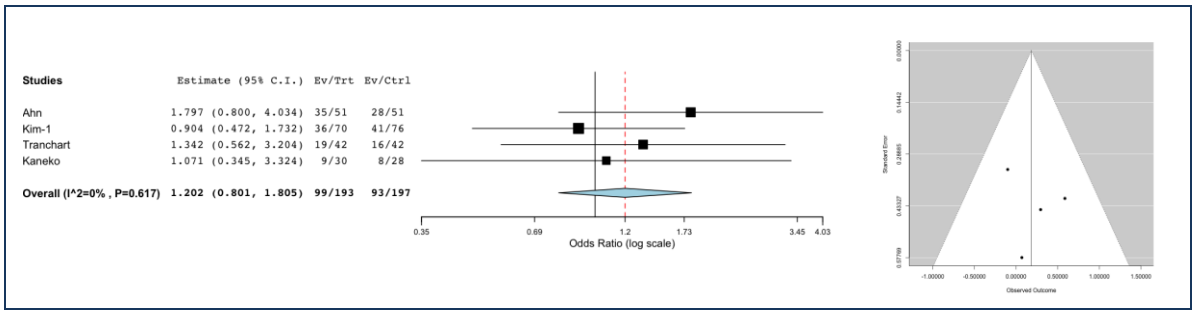


Figure 24. Solitary tumors. 5-y disease-free Survival. Heterogeneity p= 0.617; I^2 = 0%; OR 1.202 [95% CI 0.801–1.805]; p =0.375

5.5.2. Child-Pugh A Resections

Five studies including 172 open procedures and 149 laparoscopic procedures were analyzed (Table 15).

Both complication rates (heterogeneity p-value <0.001; I-squared = 81%; OR 0.256 [95% CI 0.066–0.446]; p = 0.008) and hospital stay (heterogeneity p-value ≤ 0.001; I-squared = 87%; SMD -1.037 [95% CI -1.718 to -0.357]; p = 0.003) favored a laparoscopic approach. The rest of variables evaluated do not show significant differences with respect to the open approach group (Figures 25-30).

Perioperative mortality was equivalent in both the open and laparoscopic approach (Figure 31). Long-term outcomes were insufficiently reported, and hence only three manuscripts were analyzed. These demonstrated no difference in 5 years OS and disease-free survival (DFS) rates between the two groups (Figures 32,33)

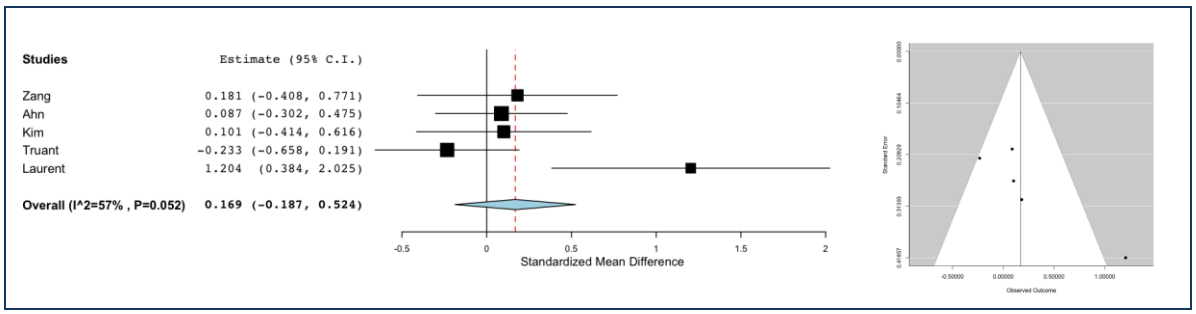


Figure 25. Child-Pugh A resections. Operative time. Heterogeneity p = 0.052; I^2 = 57%; [SMD] -0.169 [95% CI -0.187 to 0.524]; p=0.353

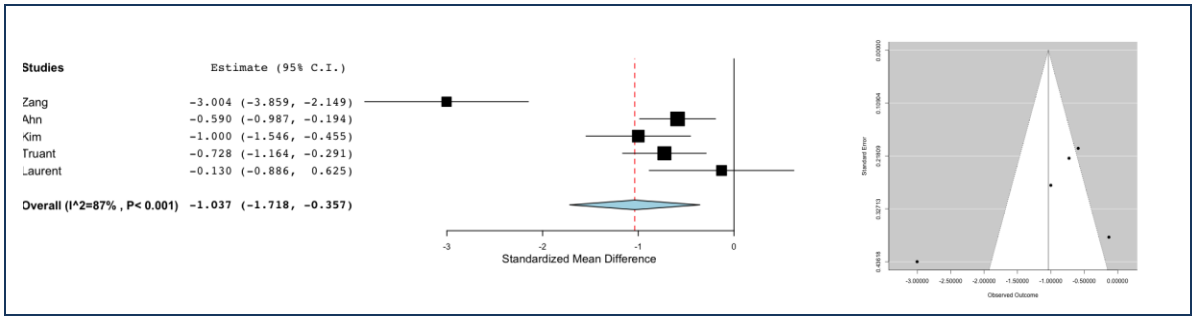


Figure 26. Child-Pugh A resections. Hospital Stay. Heterogeneity p≤ 0.001; I^2= 87%; SMD -1.037 [95% CI -1.718 to -0.357]; p = 0.003

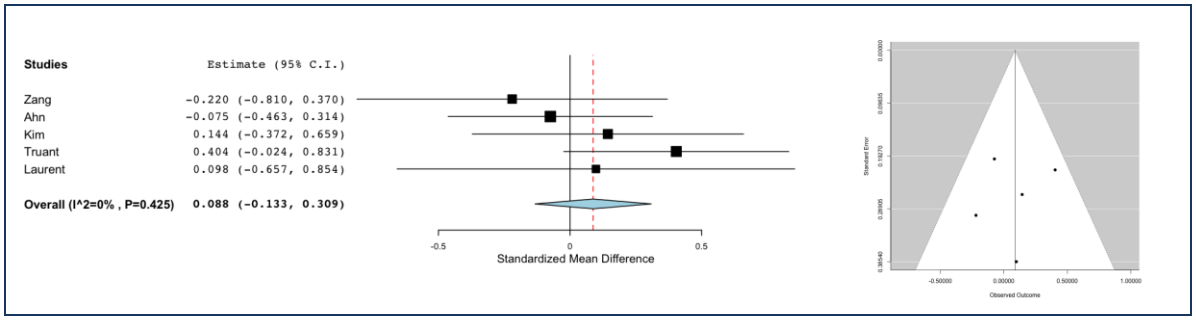


Figure 27. Child-Pugh A resections. Mean resection margin. Heterogeneity p=0.425; I^2= 0%; SMD 0.088 [95% CI -0.133 to 0.309]; p = 0.437

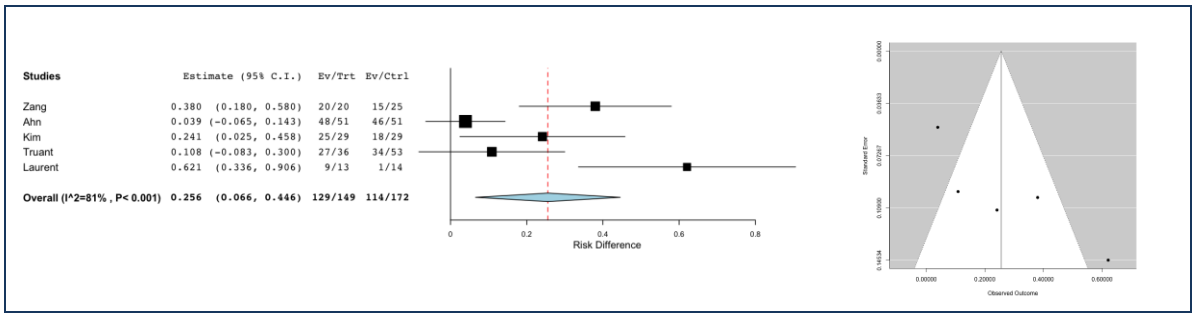


Figure 28. Child-Pugh A resections. Complications. Heterogeneity p<0.001; I^2= 81%; OR 0.256 [95% CI 0.066–0.446]; p = 0.008

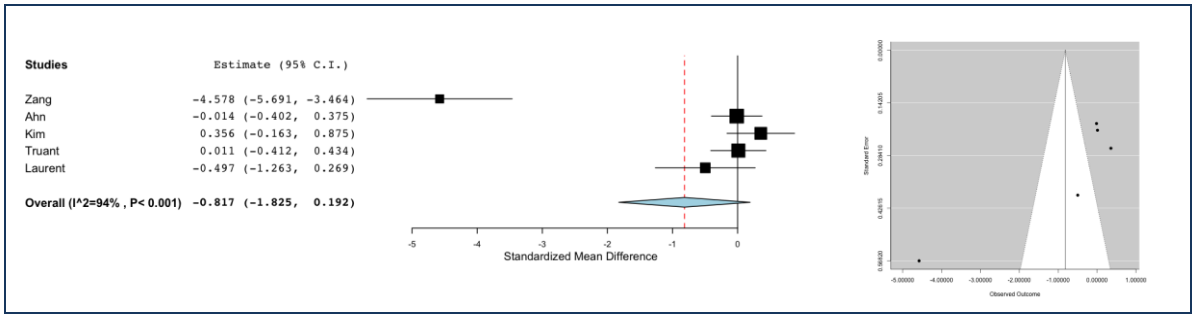


Figure 29. Child-Pugh A resections. Blood loss. Heterogeneity p<0.001; I^2 = 94%; SMD -0.817 [95% CI -1.825 to 0.192]; p = 0.112

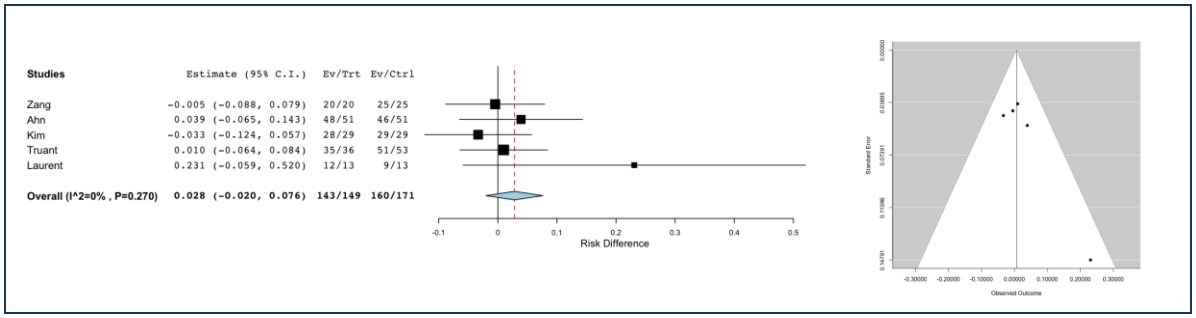


Figure 30. Child-Pugh A resections. Transfusions. Heterogeneity p=0.270; I^2 = 0%; OR 0.028 [95% CI -0.020 to 0.076]; p = 0.255

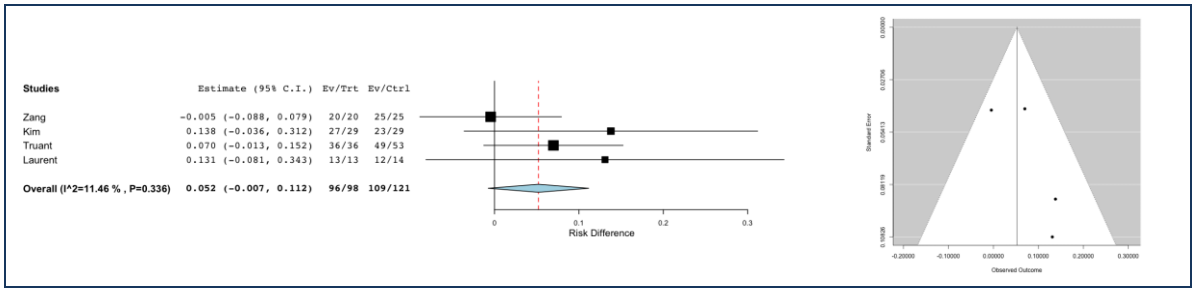


Figure 31. Child-Pugh A resections. Mortality. Heterogeneity p=0.336; I^2 = 11%; OR 0.052 [95% CI -0.007 to 0.112]; p = 0.086

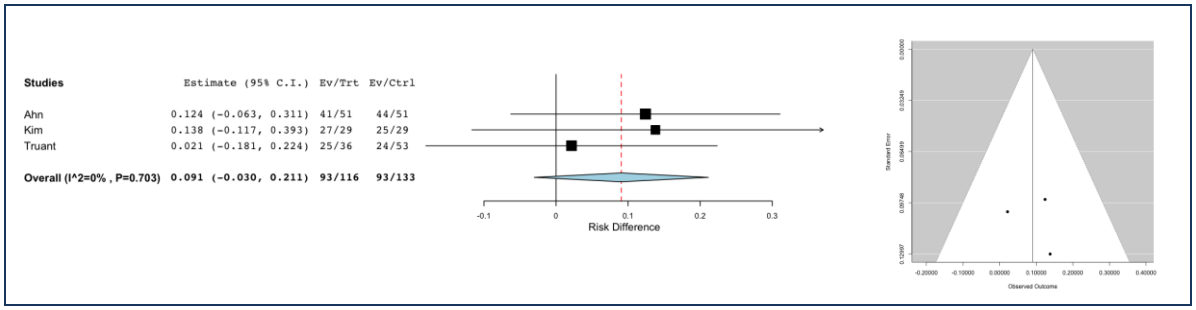


Figure 32. Child-Pugh A resections. 5-y overall Survival. Heterogeneity p=0.703; I^2 = 0%; OR 0.091 [95% CI -0.030 to 0.211]; p = 0.142

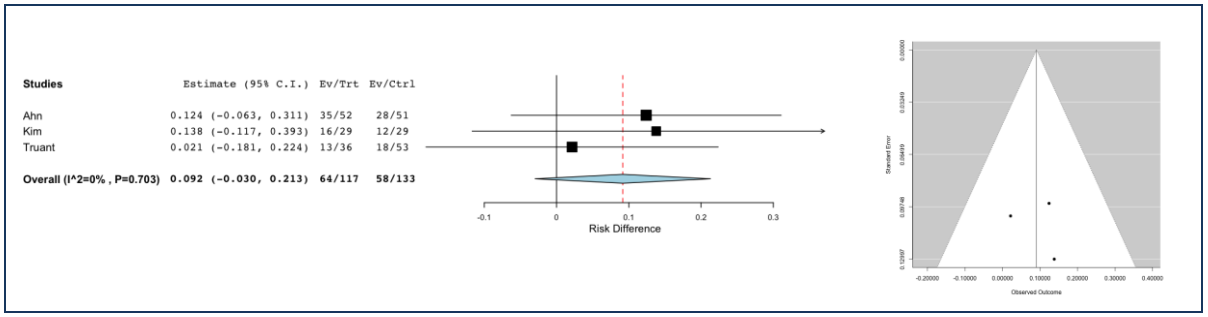


Figure 33. Child-Pugh A resections. 5-y disease-free Survival. Heterogeneity p=0.703; I^2 = 0%; OR 0.092 [95% CI -0.030 to 0.213]; p = 0.139

Perioperative mortality was equivalent in both the open and laparoscopic approach (Figure 31). Long-term outcomes were insufficiently reported, and hence only three manuscripts were analyzed. These demonstrated no difference in 5 years OS and disease-free survival (DFS) rates between the two groups (Figures 32,33)

5.5.3. Minor-Only Liver Resections

Sixteen manuscripts were identified that included 628 open procedures and 658 laparoscopic procedures (Table 15).

The short-term outcomes for complication rates (heterogeneity p-value <0.001; I-squared = 75%; OR 0.175 [95% CI 0.093–0.257]; p <0.001), blood loss (heterogeneity p-value ≤0.001; I-squared = 85%; SMD -0.685 [95% CI -1.012 to -0.357]; p <0.001), transfusión rate (heterogeneity p-value = 0.13; I-squared = 20%; OR 0.027 [95% CI 0.001–0.053]; p <0.001), and hospital stay (heterogeneity p-value ≤0.001; I-squared = 75%; SMD -0.837 [95% CI -1.083 to -0.590]; p<0.001) all favored a laparoscopic approach, with no difference in operative time and resection margin (Figures 34 to 39).

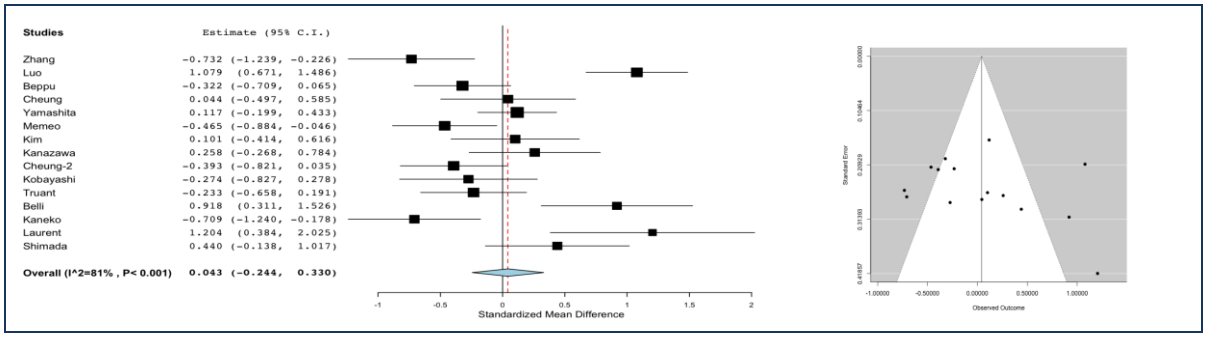


Figure 34. Minor-only liver resections. Operative time. Heterogeneity p<0.001; I^2 = 81%; SMD -0.043 [95% CI -0.244 to 0.330]; p = 0.770

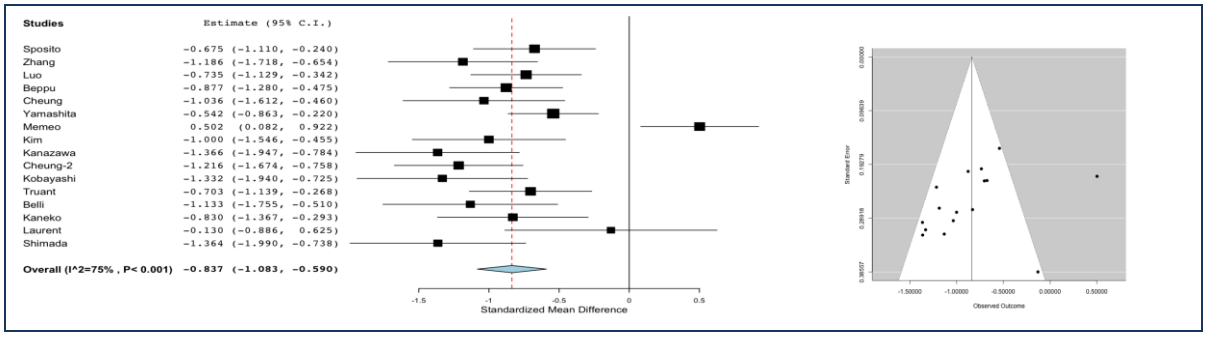


Figure 35. Minor-only liver resections. Hospital Stay. Heterogeneity p≤0.001; I^2 = 75%; SMD -0.837 [95% CI -1.083 to -0.590]; p<0.001

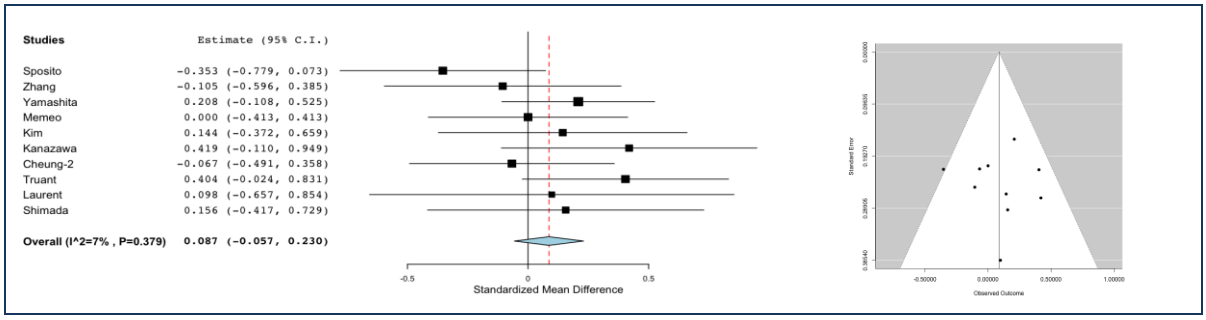


Figure 36. Minor-only liver resections. Mean resection margin. Heterogeneity p=0.379; I^2 = 7%; SMD -0.087 [95% CI -0.057 to 0.230]; p=0.236

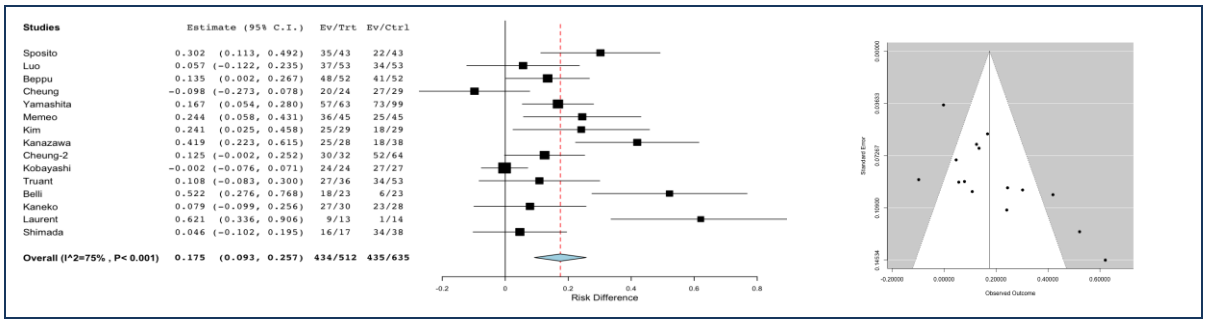


Figure 37. Minor-only liver resections. Complications. Heterogeneity p<0.001; I2= 75%; OR 0.175 [95% CI 0.093–0.257]; p <0.001

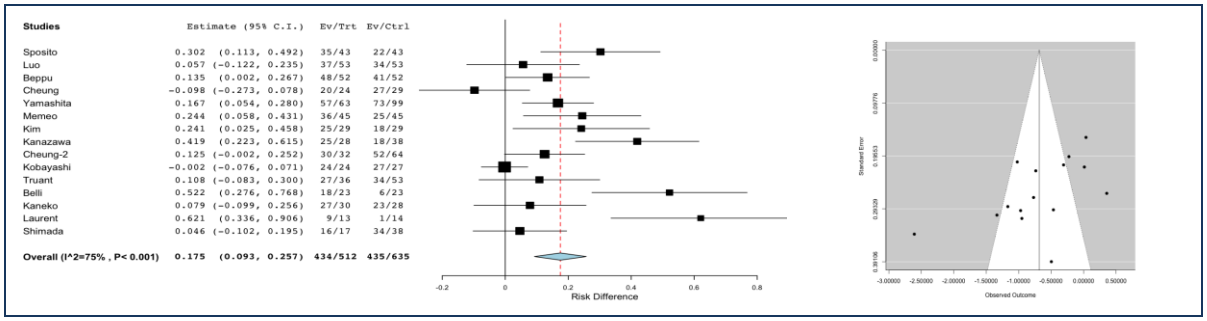


Figure 38. Minor-only liver resections. Blood loss. Heterogeneity p≤0.001; I^2 = 85%; SMD -0.685 [95% CI -1.012 to -0.357]; p <0.001

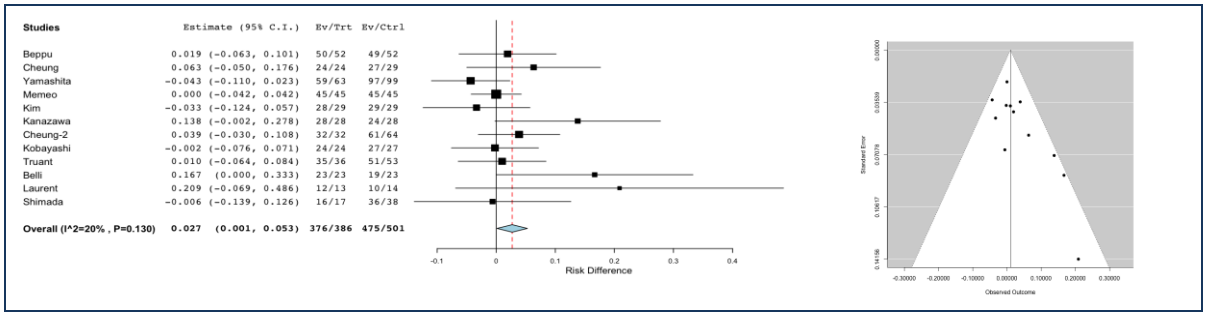


Figure 39. Minor-only liver resections. Transfusions. Heterogeneity p= 0.13; I^2 = 20%; OR 0.027 [95% CI 0.001–0.053]; p <0.001

Mortality and PHLF were not different between the groups (Figure 40 to 41), similar to the behaviour in solitary resections. Long-term outcomes (Figures 42 to 47) were similar between both approaches, except for the 1-year DFS (heterogeneity p-value = 0.019; I- squared = 66%; OR 0.133 p <0.048), which was in favor of the laparoscopic approach.

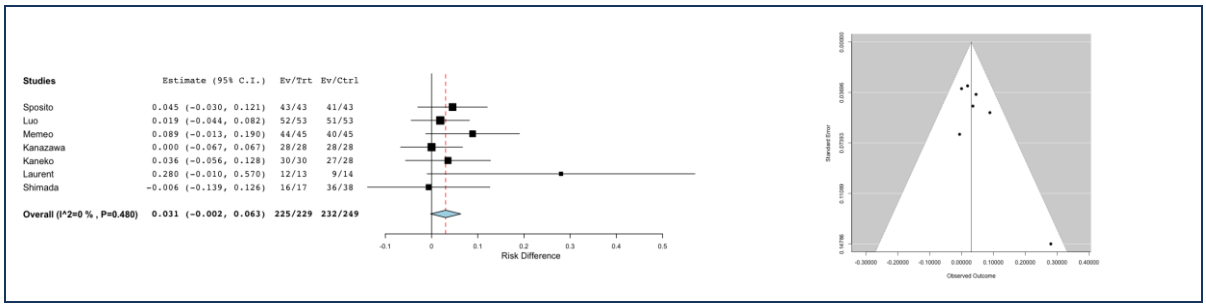


Figure 40. Minor-only liver resections. Posthepatectomy liver failure. Heterogeneity p= 0.480; I^2 = 0%; OR 0.031 [95% CI -0.002–0.063]; p =0.067

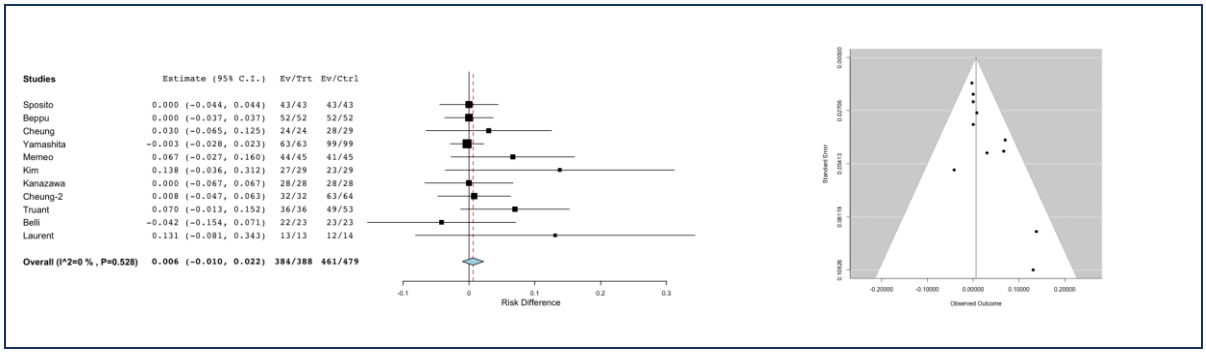


Figure 41. Minor-only liver resections. Mortality. Heterogeneity p= 0.528; I^2 = 0%; OR 0.006 [95% CI -0.010–0.022]; p =0.454

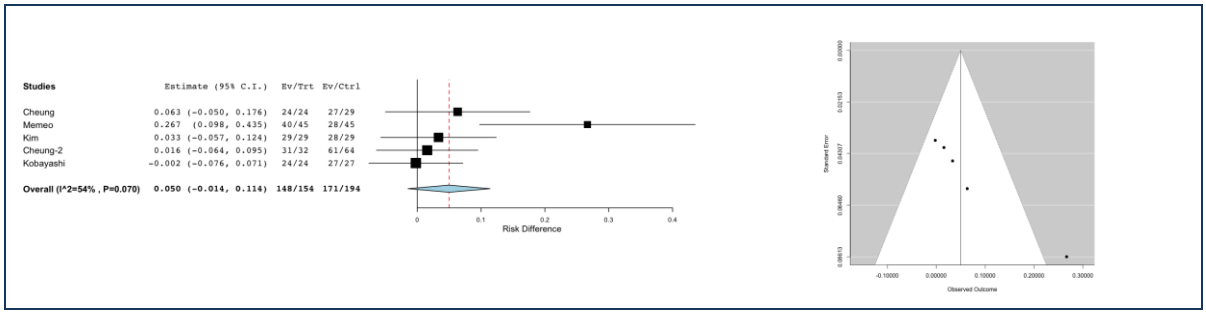


Figure 42. Minor-only liver resections. 1-y overall Survival. Heterogeneity p= 0.07; I^2 = 54%; OR 0.050 [95% CI -0.014–0.114]; p =0.129

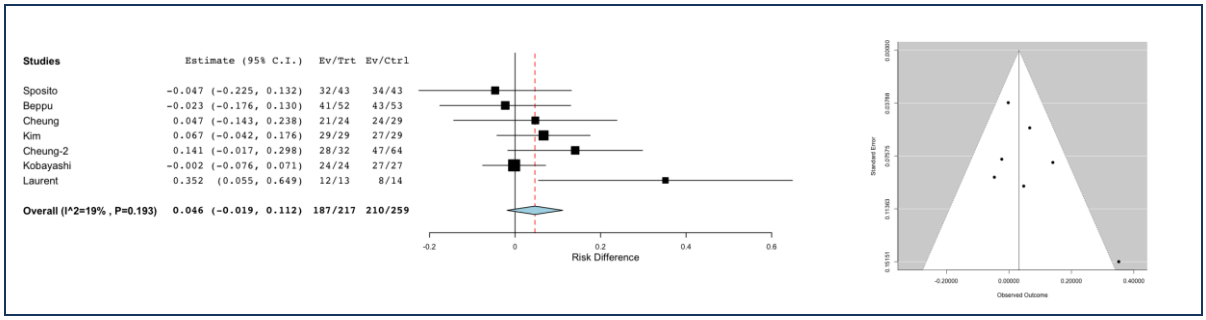


Figure 43. Minor-only liver resections. 3-y overall Survival. Heterogeneity p= 0.193; I^2 = 19%; OR 0.046 [95% CI -0.019–0.112]; p =0.162

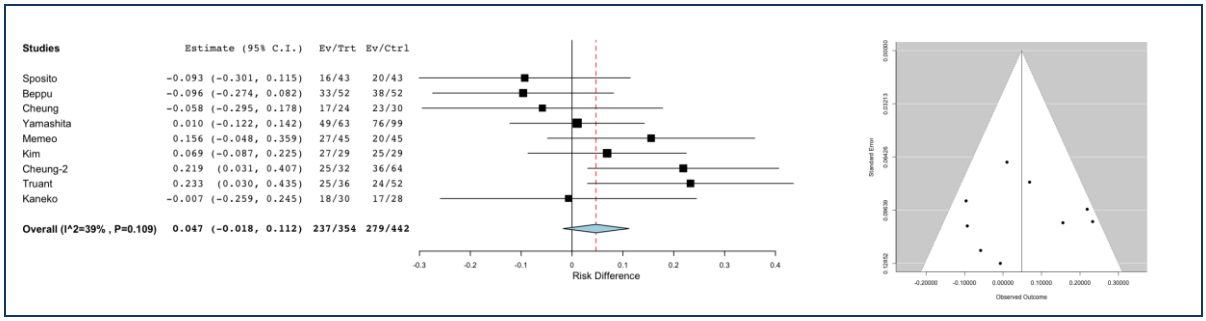


Figure 44. Minor-only liver resections. 5-y overall Survival. Heterogeneity p= 0.109; I^2 = 39%; OR 0.047 [95% CI -0.018–0.112]; p =0.154

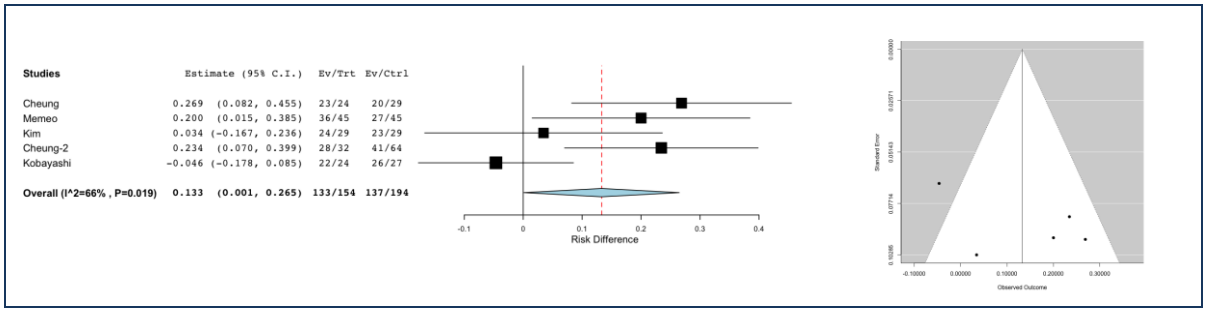


Figure 45. Minor-only liver resections. 1-y disease-free Survival. Heterogeneity p= 0.019; I^2 = 66%; OR 0.133 [95% CI 0.001–0.265]; p =0.048

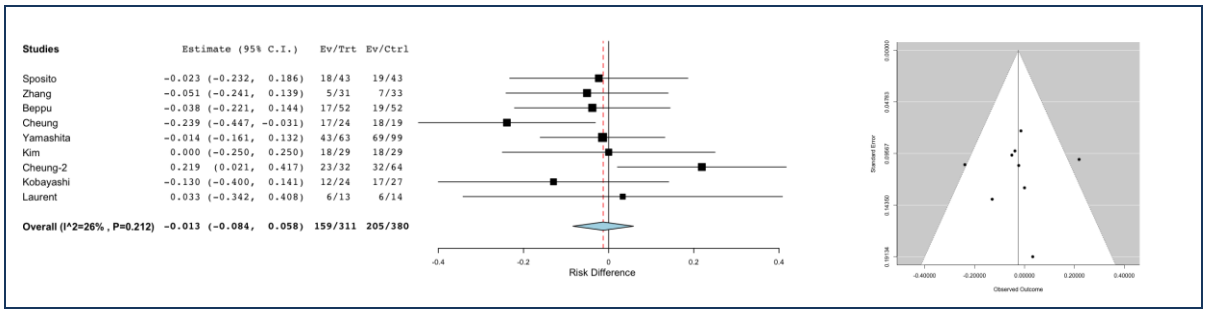


Figure 46. Minor-only liver resections. 3-y disease-free Survival. Heterogeneity p= 0.212; I^2 = 26%; OR -0.013 [95% CI -0.084–0.058]; p =0.723

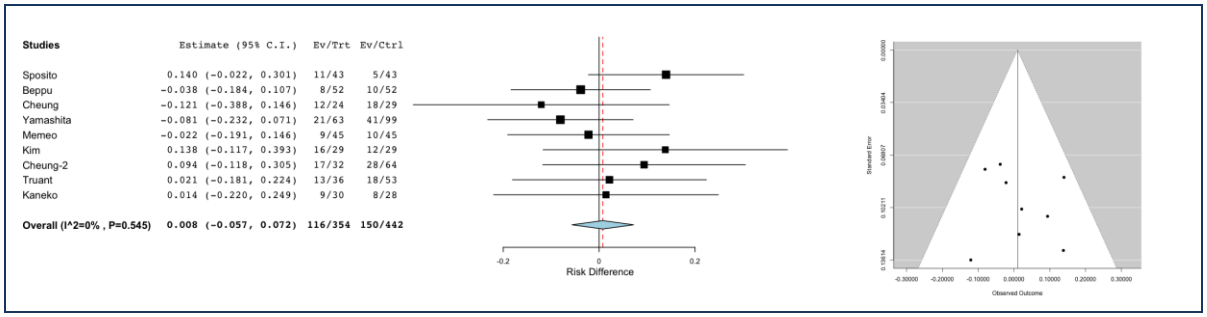


Figure 47. Minor-only liver resections. 5-y disease-free Survival. Heterogeneity p= 0.545; I^2 = 0%; OR 0.008 [95% CI -0.057–0.072]; p =0.816

5.5.4. Major-Only Liver Resections

Only limited data were available for major liver resections and no long-term data could be retrieved (Table 15).

Regarding short-term outcomes, the complication rate was lower when using a laparoscopic approach (heterogeneity p-value = 0.232; I-squared = 31%; OR 0.277 [95% CI 0.149–0.406]; p <0.001). However, operative time was shorter for OLR (heterogeneity p-value = 0.015; I-squared = 76%; SMD 0.835 [95% CI 0.155–1.516]; p = 0.016). There was a trend towards a shorter hospital stay in the laparoscopic group, but this did not reach statistical significance (Figure 48 to 50).

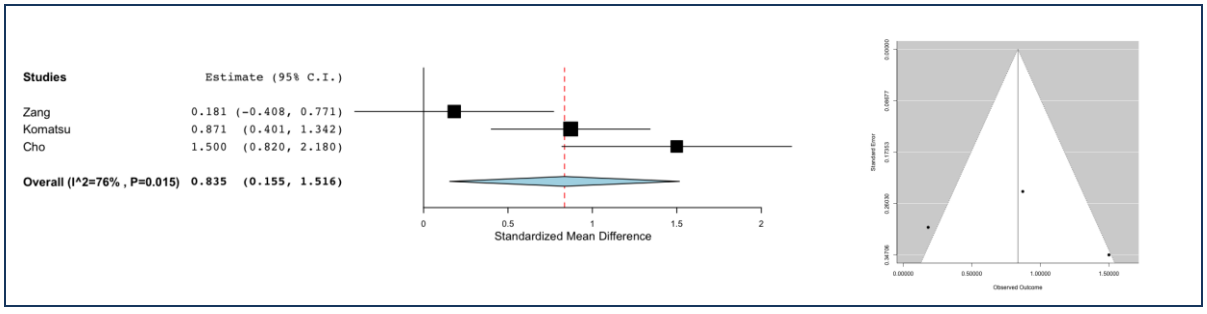


Figure 48. Major-only liver resections. Operative time. Heterogeneity p= 0.015; I^2 = 76%; SMD 0.835 [95% CI 0.155–1.516]; p = 0.016

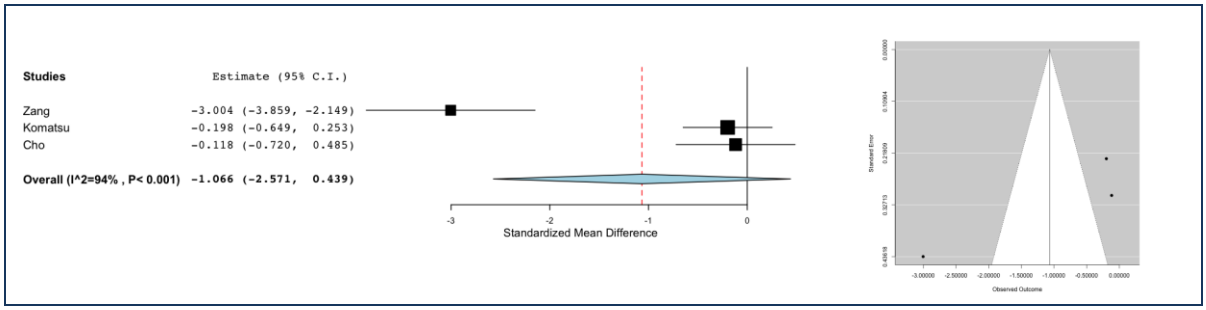


Figure 49. Major-only liver resections. Hospital Stay. Heterogeneity p<0.001; I^2 = 94%; SMD -1.066 [95% CI -2.571 to 0.439]; p = 0.165

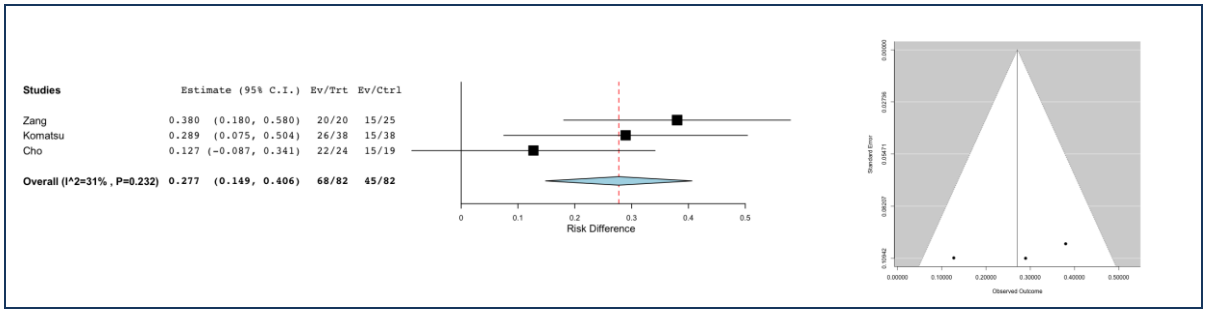


Figure 50. Major-only liver resections. Complications. Heterogeneity p= 0.232; I^2 = 31%; OR 0.277 [95% CI 0.149–0.406]; p <0.001

In the other items (margin resection, transfusions rate and blood loss) the analysis could not be performed because only two papers (80) (81) had data available, therefore the sample was not sufficient enough. In the major-only resections group, mortality and PHLF were not calculated due to insufficient data. The same problem occurs with long-term results where data could not be obtained.

5.5.5. Combined Resections

The three manuscripts that contained combined studies did not have any long-term data available (Table 15).

Regarding short-term outcomes, the rate of complications (heterogeneity p value = 0.469; I-squared = 0%; OR 0.076 [95% CI 0.036–0.115]; p <0.001) and hospital stay (heterogeneity p-value ≤0.001; I-squared = 92%; SMD -0.788 [95% CI -1.339 to -0.237]; p =0.005) favored a laparoscopic approach, but the remaining short-term outcomes (operative time and blood loss) were not different to the open approach (Figures 51 to 54).

In the other items (margin resection and transfusions rate) the analysis could not be performed because only two papers had data available, therefore insufficient information existed. Regarding post-hepatectomy liver failure and mortality rate the results are not available due to insufficient data. As with long-term outcomes, the data available for calculation was also insufficient.

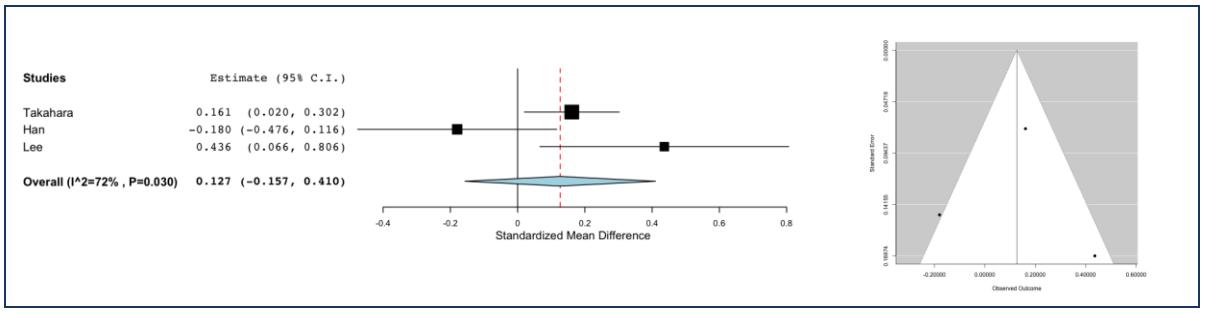


Figure 51. Combined resections. Operative time. Heterogeneity p= 0.030; I^2 = 72%; SMD 0.127 [95% CI -0.157 to 0.410]; p = 0.381

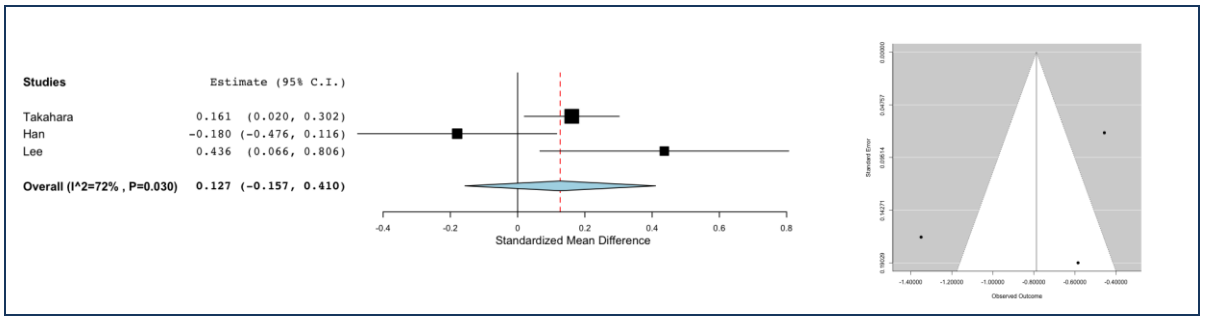


Figure 52. Combined resections. Hospital stay. Heterogeneity p≤0.001; I^2 = 92%; SMD -0.788 [95% CI -1.339 to -0.237]; p = 0.005

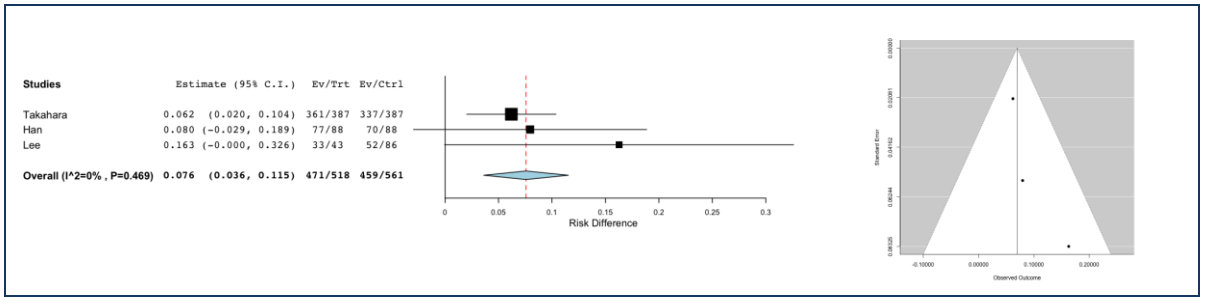


Figure 53. Combined resections. Complications. Heterogeneity p= 0.469; I^2 = 0%; OR 0.076 [95% CI 0.036–0.115]; p < 0.001

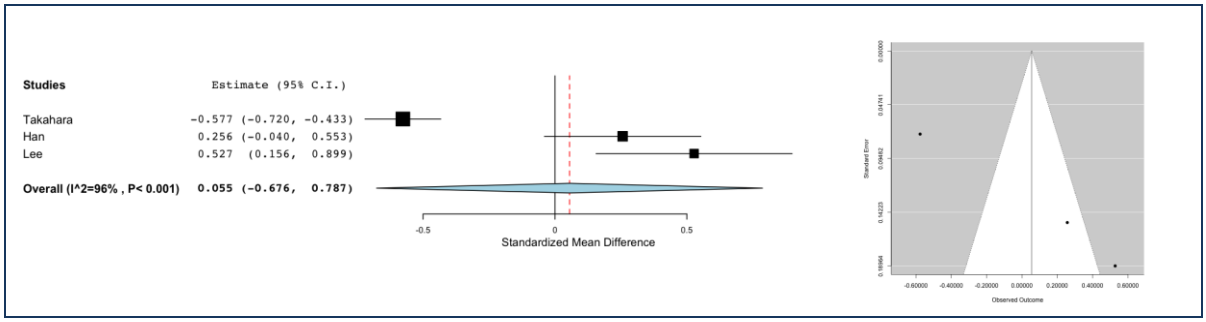


Figure 54. Combined resections. Blood loss. Heterogeneity p<0.001; I^2 = 96%; SMD 0.055 [95% CI -0.676 to 0.787]; p = 0.883

Then, summay tables where short-term results are represented by Forests Plot were created. The sense of statistical significance might be observed through the red, green or yellow colour, in favour of open, laparoscopic approach or without significance differences respectively.

A single significant statistically difference is found in favour of the open approach. This is the case of major liver resections in which the operative time is shorter than in the laparoscopic approach group. However, a lower complication rate is observed under laparoscopic approach in the 5 subgroups analyzed (Figures 55 to 58)

Data from short-outcomes and long-outcomes are shown in Table 16, considering if they were statiscally significant towards open of laparoscopic approach.

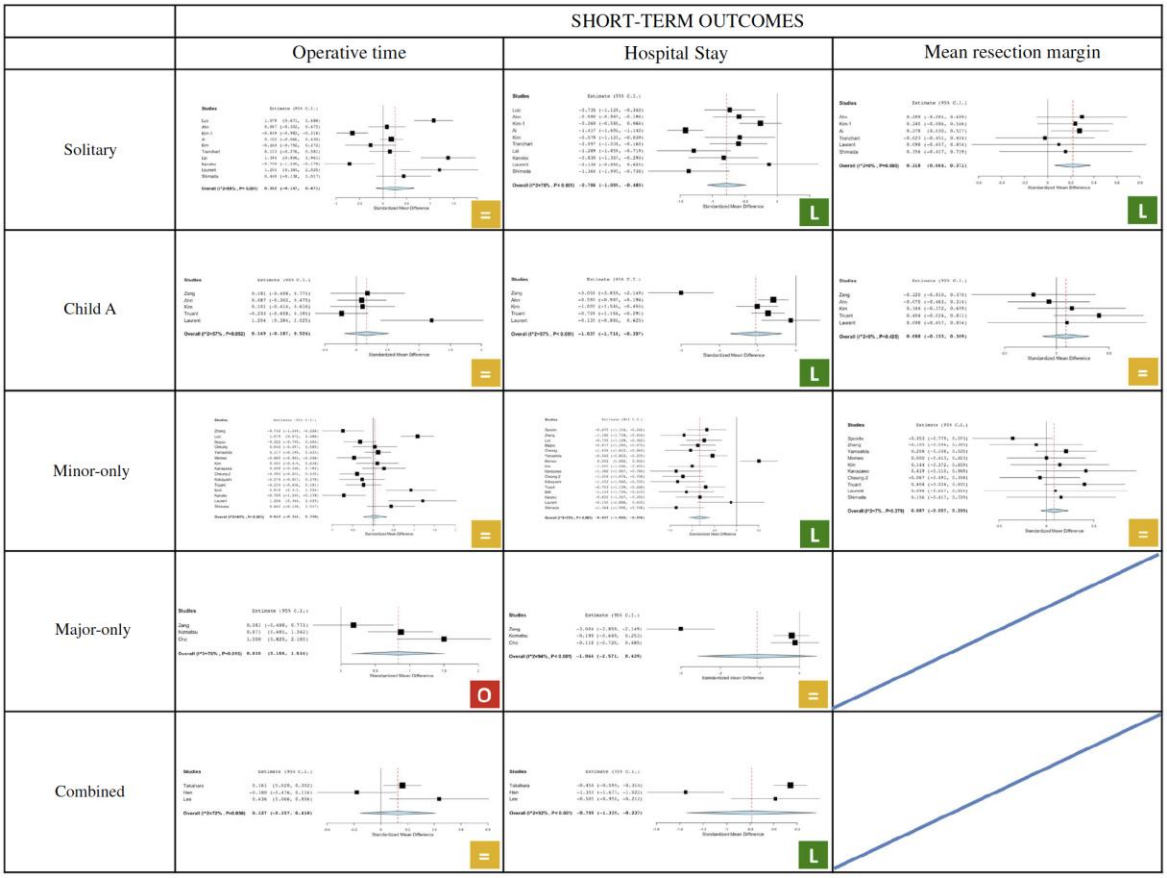


Figure 55. Meta-analysis of short-term outcomes (I)

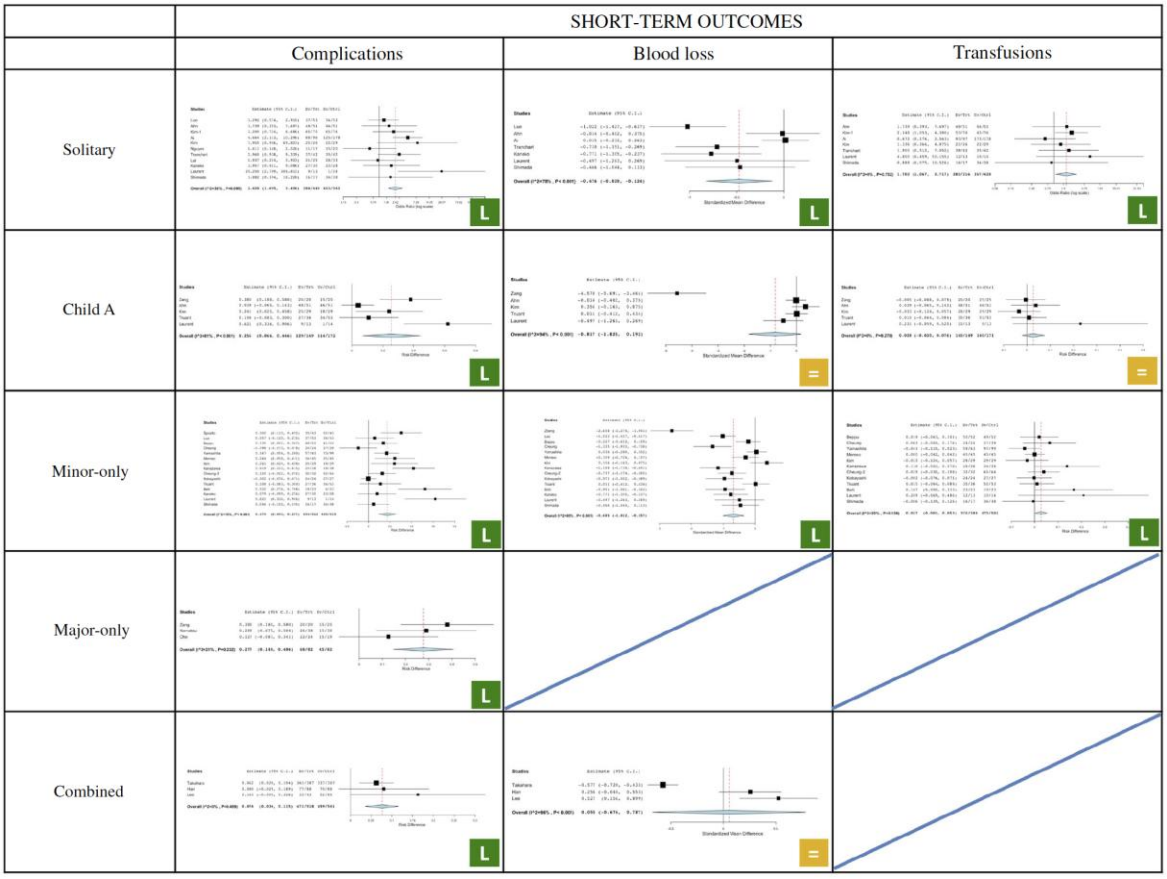


Figure 56. Meta-analysis of short-term outcomes (II)

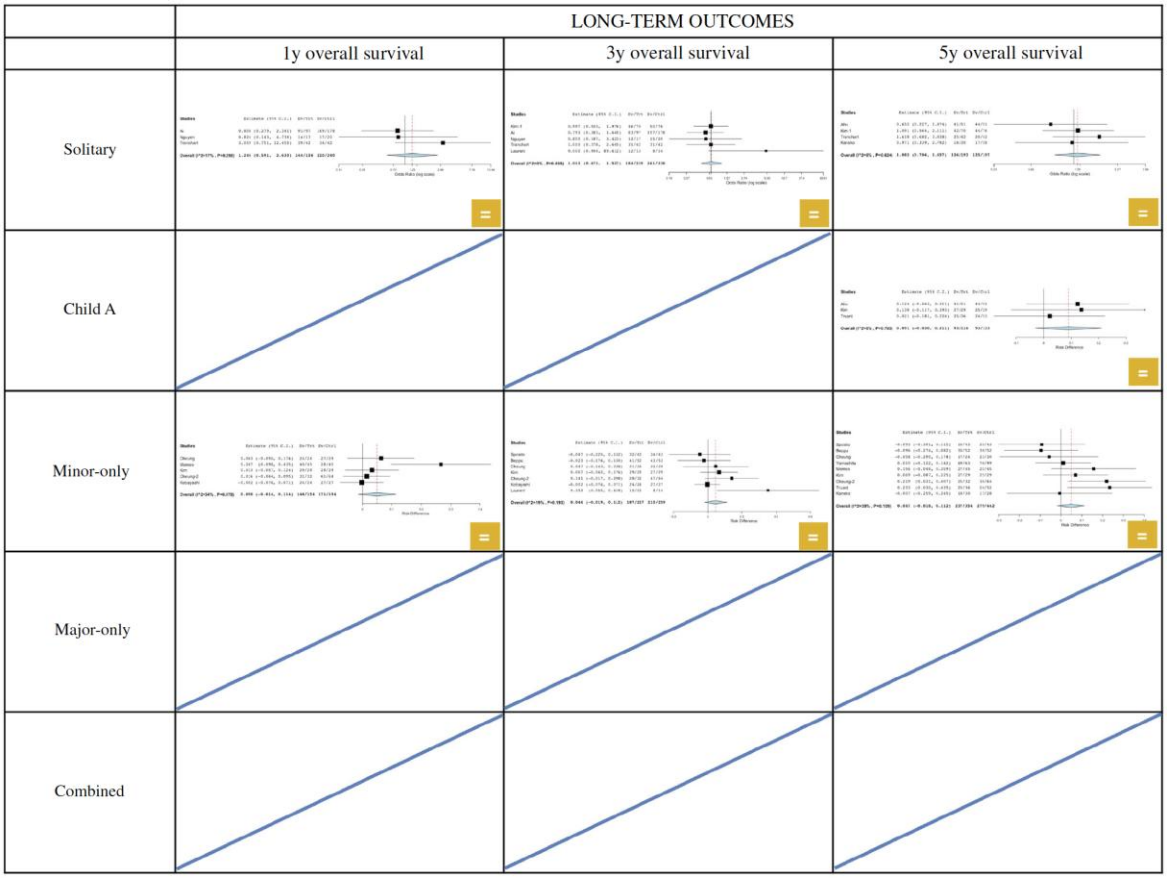


Figure 57. Meta-analysis of long-term outcomes (I)

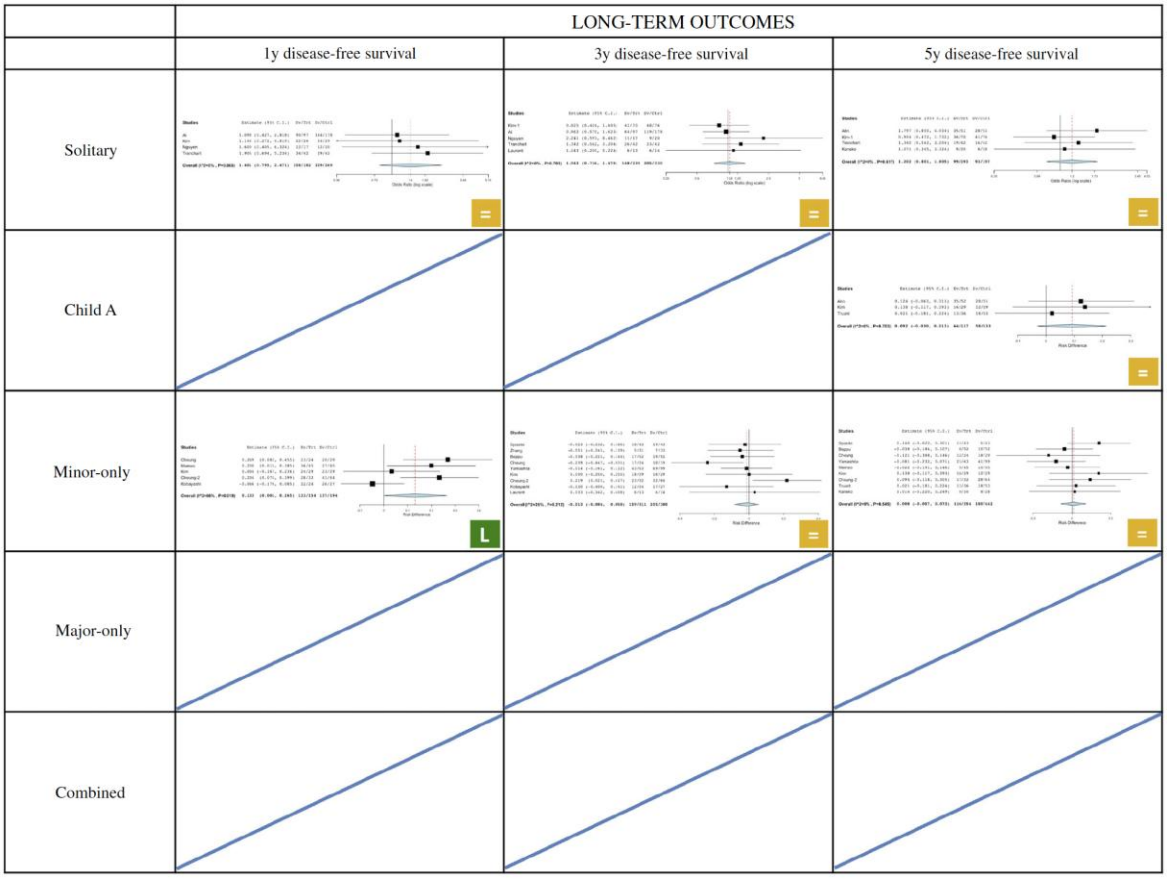


Figure 58. Meta-analysis of long-term outcomes (II)

Table 16. Summary of short and long outcomes in each subgroup analyzed. If results were statistically significant towards open approach they are shown in red, and green for laparoscopic approach. If no significant differences were found, results are shown in yellow.

Solitary Tumors	**Favors Open Approach**	**Equivalent**	**Favors Lap Approach**
Operative time		√	
Hospital stay			√
Mean resection margin			√
Complications			√
Blood loss			√
Transfusion			√
Posthepatectomy liver failure		√	
Mortality		√	
1-y Overall survival		√	
3-y Overall survival		√	
5-y Overall survival		√	
1-y Disease free survival		√	
3-y Disease free survival		√	
5-y Disease free survival		√	
Child-Pugh A resections			
Operative time		√	
Hospital stay			√
Mean resection margin		√	
Complications			√
Blood loss		√	
Transfusion		√	
Mortality		√	
5-y Overall survival		√	
5-y Disease free survival		√	
Minor-only resections			
Operative time		√	
Hospital stay			√
Mean resection margin		√	
Complications			√
Blood loss			√
Transfusions			√
Posthepatectomy liver failure		√	
Mortality		√	
1-y Overall Survival		√	
3-y Overall Survival		√	
5-y Overall Survival		√	
1-y disease-free Survival			√
3-y disease-free Survival		√	
5-y disease-free Survival		√	
Major-only liver resections			
Operative time	√		
Hospital stay		√	
Complications			√
Combined resections			
Operative time		√	
Hospital stay			√
Complications			√
Blood loss		√	

6. DISCUSSION

Minimally invasive approaches have completely transformed the conception of surgery over the past 2 decades. In many cases, the laparoscopic approach is considered as the standard of practice (126) (127) (128) (129) (130) (131) (132) (133) (134).

Patients diagnosed of liver tumors who are considerd for surgery are complex as most of them may have undergone extensive chemotherapy (in metastasic liver disease) or may have any kind of underlying liver disease (hepatitis, fibrosis or cirrhosis). Certainly, case-by-case evaluations are required, and it should be emphasized that open and laparoscopic techniques should not be opposed but considered as complementary. They can even be associated with the same patient by hybrid procedures.

A recent extensive worldwide review and the results from its meta-analysis suggest that laparoscopic liver surgery might be considered a safe alternative to the open traditional approach that should be offered to a growing proportion of selected patients (48).

This was the largest meta-analysis to date (48), and it suggests that a significant proportion of LLRs are performed for the management of HCC, as 3072 out of 6190 LLRs for malignancies were performed for HCC. Up to this date, different comparative studies and case series have been published with a higher or lower level of evidence. There are few publications focused on LLR for HCC.

HCC resection is normally performed on patients with cirrhotic livers, with a complication index greater than in resections on healthier livers. All this leads to a difficult extrapolation of the results published in the current literature for this type of resection. For this reason, a study with a high methodological level was necessary in order to focus on HCC resections and study if the benefits of the laparoscopic approach on liver resections could also be obtained in cirrhotic livers.

6.1. Literature Discussion

In 2017, Southampton hosted the EGMLLS, with the specific aim of presenting and validating the first set of evidence-based guidelines for laparoscopic liver surgeons (135). In this setting, the aim of our study was to perform a high-quality systematic review and meta-analysis examining the short- and long-term outcomes of LLR for HCC.

Previous meta-analyses have already reported the results of open resection versus LLR for HCC (136) (137) (72) (138) (63) (68) (113).

Twaij (63) performed a systematic review and meta-analysis based on 4 studies with an acceptable level of evidence. The aim was to review the currently available data comparing LR vs OR for HCC in patients with known cirrhosis. The risk of bias was assessed using NOS with acceptable quality (7 and 8 out of 9).

All studies included were single centre retrospective studies. The limitations of this manuscript were: a small number of studies with no randomized trials, tumor size was not reported and neither patients demographics data. Twaij suggests that a laparoscopic approach, compared to open surgery, might result in improved short-term outcomes considering wider resection margins, reduced intraoperative blood loss and need for transfusions, as well as reduced morbidity rates and shorter lengths of stay.

A year later, Leong published a systematic review (including 17 comparative studies) and a comparative study in their hospital (113) with better level of evidence. Their analysis of the 17 studies showed that the rates of postoperative complications were significantly lower in patients who underwent LLR. The studies included were specific to HCC patients with underlying CLD or cirrhosis, showing that LLR resulted in fewer postoperative complications compared to OLR.

Leong found, as in our study, a significant increase in disease-free survival rates in the LLR group; this could be attributed to the higher incidence of microscopic vascular invasion found on histology in the OLR group, which is a significant underlying risk factor for tumor recurrence.

This systematic review had some limitations, which warrant discussion and should be considered when interpreting the results. Selection of patients in both the LLR and OLR groups followed certain criteria based on the pre-operative clinicopathologic characteristics of each case, as well as according to the experience and expertise of the surgeons (selection bias). Leong concluded that as a curative treatment for HCC, LLR provides better short-term outcomes than OLR in terms of intraoperative blood loss, blood transfusions, and length of hospital stay, while both LLR and OLR provide similar long-term oncologic outcomes.

The last meta-analysis reported was published by Chen (68) and was based on 7 retrospective studies. NOS was used to assess the risk of bias for quality assessment of non-randomized studies. The overall quality of this study was good (NOS score 7 out of 9) with a high-quality evidence level.

Chen (68) found wider tumor margin, similar operating time, less blood loss, less transfusion rate, lower postoperative morbility, similar postoperative mortality, similar curative resection and shorter hospital stay in the laparoscopic approach vs the open approach. Regarding long-term results, the overall survival rate at 1 year was similar, but at 5 years in LH it seemed to be significantly higher than in OH (RR=1.28, 95% CI 1.01 to 1.62, p=0.04, i^2 =62%). Similar disease-free survival rates at 1-, 3- and 5-years were found.

The limitations of this study are similar to the ones in previous studies. All studies are retrospective, non-randomized, which could increase the selection bias. The sample size is small, so it decreases the reliability of the final results. The patients in OH had huge HCC, higher degree of cirrhosis and difficult locations, leading to an increased risk of blood loss (selection bias).

Cipriani et al. (138) published a recent interesting manuscript comparing results in cirrhotic vs non-cirrhotic liver, showing the advantages of the laparoscopic approach in liver resections and assessing the impact of the laparoscopic approach in the specific setting of chronic liver disease with impaired liver function.

This study shows a similar complication rate in the cirrhotic and non-cirrhotic liver, also in the development of ascites or liver failure. Comparing the obtained complication rate (10-30%), a reduction in the complication rate of the laparoscopic approach versus open in cirrhotic livers could be observed.

The study also shows a subanalysis between Child A and Child B with similar mortality and morbidity rates. The findings are of major importance, as it is still presumed that the specific advantages of LLR might remain restricted to patients with compensated cirrhosis. It is suggested that laparoscopy may offer a protective effect with regards to postoperative liver failure and ascites, even in Child B patients (138). They propose that the lower fluid requirement, the preservation of collateral circulation and the minimum hepatic mobilization would explain the lower rate of decompensation in patients undergoing laparoscopic approach.

The previous meta-analyses have already reported the results of open resection versus LLR for HCC; however, most of them focused only on short-term outcomes. Only the studies by Zhou et al. (136) and Fancellu et al. (137) analysed long-term OS and DFS (both in 2011), including few reports in which different types of resection were mixed.

The study of Zhou (136) shows one of the most complete analysis of long-term outcomes with survival rates and morbidity at 3-5 years (3-6 studies). No significant differences were found between the groups regarding pathologic resection margins, overall survival and disease-free survival rates. Nine out of ten studies showed no recurrences related to laparoscopy, recurrences such as peritoneal dissemination and port-site recurrences, were not observed in the laparoscopic group.

In our study, short- and long-term outcomes for each category identified have been matched with the intention of increasing the evidence of the currently available results. A subgroup meta-analyses specifically examining patients with Child-Pugh A cirrhosis, solitary tumors, and those

undergoing minor and major liver resections have been performed in the study.

This detail of performing subgroup analysis is based on the ability to obtain conclusions for each type of liver and patient resection. Therefore, those patients with HCC in which the laparoscopic approach would be indicated could be selected.

Additional literature searches were performed for "portal hypertension" (using platelet count and/or esophageal varices), multicentric HCC, Barcelona Liver Clinic (BCLC)-A or –B, or severe cirrhosis, but not enough comparative series were available.

In the near future, with the advance and extension of laparoscopic surgery, a greater number of resections will be carried out on cirrhotic livers. Therefore, future studies might be carried out with a greater number of resections that could lead to more specific and detailed conclusions for each type of LLR or patients profiles.

6.2. Methodological Discussion

In 1992 the "Evidence-Based Medicine Working Group" introduced the concept of Evidence-Based Medicine (MBE) for the first time (139). Since that time, medical practice has undergone dramatic changes where clinical decisions are based on the best existing evidence judged from its methodological quality and not only on the experience of the attending physician (140).

There are multiple biases that must be taken into account when performing meta-analyses. Among these, researchers only consider publication bias, while other types of biases are ignored or not taken into account. Publication bias is basically related to the publication itself and not to the data obtained in a scientific research study. So this bias represents a risk to the validity of meta-analyses due to selective publication based on its findings (141).

There are many ways to assess publication bias. The publication bias is derived from the fact that many scientific works, mostly with "negative" results (those that do not find significant differences or with results against the hypothesis of study or the usual established) never get published, take longer to do so or are less cited in other publications. This fact may have an impact on the results of a bibliographic search and can lead to biased results in a meta-analysis. Other factors that may contribute to this type of bias are the duplicate publication of studies or the disregard of works published in a language other than English (142).

In our case, the graphic method of Light and Pillemer (funnel plot) where a graph is calculated using the effect sizes and sample sizes of each study was used. From this graph, the possibility of publication bias can be examined. In our study, although there are a limited number of studies in certain subcategories, it can be visually observed how a high publication bias can not be detected.

The represented point cloud does not deform the funnel plot and does not lose its symmetry since small studies are not arranged towards the right side with respect to the central estimator. However, this graphic technique has some limitations such as some subjectivity and difficulty in its interpretation, mostly where there are few studies, which is the normal circumstance.

A secondary test for the measurement of heterogeinity was considered in our statistical method. The I^2 statistic describes the percentage of variation across studies that is due to heterogeneity rather than chance (143) (144). I^2 is an intuitive and simple expression of the inconsistency of studies' results.

A confidence interval for I^2 is constructed using either i) the iterative non-central chi-squared distribution method of Hedges and Piggott (145) or ii) the test-based method of Higgins and Thompson (143). The non-central chi-square method is currently the method of choice. It is computed if the 'exact option is selected.

Choosing between fixed and random effects models

If there is very little variation between studies then I^2 will be low and a fixed effects model might be appropriate. With fixed effects all of the studies that you are trying to examine as a whole are

considered to have been conducted under similar conditions with similar subjects – in other words, the only difference between studies is their power to detect the outcome of interest. An alternative approach, 'random effects', allows the study outcomes to vary in a normal distribution between studies. Many investigators consider the random effects approach to be a more natural choice than fixed effects, for example in medical decision making contexts (146)(88)(147).

More data are required for random effects models to achieve the same statistical power as fixed effects models, and there is no 'exact' way to handle studies with small numbers when assuming random effects. This should not be a problem with most meta-analyses, however do not use random effects models with sparse datasets without expert statistical guidance.

Random effects is not a cure for difficulty in generalising the results of a meta-analysis to real-world situations. Generalisability might be explored through additional analyses that incorporate specific predictive uncertainties on top of the intrinsic uncertainties of the studies under review (147).

It should be noted that the I^2 score was high in many of the comparisons and thus lower confidence in the estimates might be considered a limitation to our manuscript.

In order to minimize this limitation, our meta-analysis included several steps that tried to minimize biases. As per the EGMLLS methodology, we initially performed an extensive literature review with strong quality discrimination.

For this purpose, we used two well-validated quality assessment tools to obtain the best quality of evidence. Firstly, the SIGN methodology and the NOS manuscripts that were rated as low quality in the SIGN and/or received less than six stars in the NOS were discarded.

Secondly, we performed subgroup meta-analyses, as aforementioned, specifically examining patients with Child-Pugh A cirrhosis, solitary tumors, and those undergoing minor and major liver resections.

Finally, all meta-analyses performed to date used the methodology of Hozo et al. (148), however, we have chosen to use the methodology of Wan et al., which has recently been demonstrated to achieve more precise calculations of mean and SD, and which in turn allows for more accurate conclusions. In meta-analyses, researchers often pool the results of the sample mean and standard deviation from a set of similar clinical trials (149).

The included studies can represent their data in a different way such as minimum-maximum or first-third quartile. Hence, in order to combine results, the mean and standard deviation of the study samples must be estimated.

Wan et al. developed different scenarios with different distributions applying different approximation methods for the estimation of the sample mean and standard deviation and proposed some new estimation methods to improve the existing literature.

Wan et al. point out that the widely accepted estimator for the standard deviation proposed by Hozo et al. has some serious limitations and is always less satisfactory in practice because the estimator does not fully incorporate the sample size.

Therefore, the use of this novel method to estimate the mean and standard deviation in our analysis gives greater consistency and accuracy to our results, avoiding biases and errors that could appear when using other methods in the published meta-analyses before ours.

6.3. Discussion of results

6.3.1. Controversies in the use of minimally invasive techniques in the treatment of hepatocellular carcinoma

The three most important changes in the evolution of laparoscopic surgery were the Consensus Conferences held in Louisville, Morioka and Southampton in 2008, 2014 and 2017 respectively. It is interesting to show the evolution of the

establishment of the laparoscopic approach for the resection of hepatocellular carcinoma in cirrhotic livers.

Resection remains the first-line treatment for HCC in compensated cirrhosis in many centres. It was also recognized that anatomic resection was associated with less recurrence and better survival rates than wedge or tumorectomy resections (1). Therefore, the exponential trend that this approach has presented in recent years is obvious.

Today, laparoscopic liver surgery is a reality that keeps under a continuous progress. Therefore, an update on the worldwide situation was necessary to asses the current status of minimally invasive liver surgery (48). The largest meta-analysis to date suggested that a significant proportion of LLRs are performed for the management of HCC, as 3072 out of 6190 LLRs for malignancies were performed for HCC (48).

The data from the Louisville Consensus presented suggested that laparoscopic resection on small HCC is associated with reduced morbidity in cirrhotic patients as compared with open resection, especially with reduced occurrence of postoperative ascites.

The conclusions were that laparoscopic resections of small hepatocellular cancers in a cirrhotic liver are feasible and safe in experienced centres, and follow-up data from a French group suggested that the long-term oncologic outcome has not been compromised by the laparoscopic approach compared with open resection.

The Second International Consensus Conference on LLR was held in Morioka with the dual goal of defining the current role of LLR and developing recommendations and guidelines. The conclusions of Morioka regarding HCC were that anatomical resection for HCC is the standard of care procedure, but the laparoscopic versions of this technique need to be standardized to increase propagation.

The last consensus of Laparoscopic liver surgery was held in Southampton in 2017.In this meeting the clinical questions raised about HCC were more concrete than in previous consensus. A specific section for HCC liver resections surgery was raised in order to answer certain questions observed in the clinical practice.

The Southampton Guidelines were based on the aforementioned methodology and thus are based on published evidence and expert opinions (52). The conclusions focused on topic 3 in reference to HCC, were of great interest since for the first time they answered questions raised in case of cirrhotic patients with HCC resections.

In the previous Consensus, the conclusions drawn were ambiguous and did not present specific cases for cirrhotic livers or in what sense patients with chronic liver disease who underwent HCC resection surgery could benefit from the laparoscopic approach.

This guideline strongly suggested that LLR for HCC is associated with reduced blood loss, transfusion rate, postoperative ascites, liver failure and hospital stay with comparable operative time, disease-free margin and recurrence rates (52).

In the case of cirrhotic patients no differences in operative time, blood loss, intraoperative complications, hospital stay, and morbidity were found in LLR.

The laparoscopic approach appears to reduce the incidence of postoperative ascites, liver failure, and morbidity assessed, with no difference in overall or disease-free survival rates at 2 years (52).

These conclusions are a great step from the point of view of laparoscopic surgery. Previously, the question of whether the laparoscopic approach was dangerous in the cirrhotic liver was constant in most centres due to the complexity of these patients and the increased risk of bleeding.

Additionally, due to the complex vasculature, clotting abnormalities and development of ascites, laparoscopic resection in cirrhotic livers has taken longer to receive endorsement by the wider surgical community (63). Although higher-quality data is desirable, the currently available data suggest that laparoscopic resection of HCC in cirrhotic patients is

safe and potentially provides better outcomes for patients when compared to the open approach (84).

In this setting, the aim of our study was to perform a high-quality meta-analysis examining the short- and long-term outcomes after LLR for HCC. The results of our meta-analysis demonstrated that for most short-term outcomes, a laparoscopic approach provides better results than an open approach. In accordance with the rest of the recent meta-analyses, we can conclude that cirrhotic patients who underwent liver resections for HCC benefited from the laparoscopic approach (63) (82) (113).

Our study presents a deeper step, where a specific profile has been performed for each type of resection. Therefore, the five most common scenarios in the clinical practice can be found: Minor-resection, Major-resection, Solitary tumor, Child-Pugh A and combined resection.

As the results have been analysed in each one of the feasible scenarios, the statistical value and clinical significance of this study are higher.

The meta-analysis showed that the laparoscopic approach did better than the open approach, especially within the subgroup analyses for solitary tumors and minor resections. Similarly, the complication rate was more favourable for a laparoscopic approach in all analyses.

The results suggest that a laparoscopic approach is similar, if not better than, the open approach for the management of HCC in patients with Child-Pugh A cirrhosis, solitary tumors, and those undergoing minor resections in terms of short-term outcomes.

In modern surgical society, laparoscopic and minimally invasive surgeries have become the gold standard for many surgical procedures. Similar to other areas of surgery, this review indicates that a laparoscopic approach to hepatic resection in cirrhotic patients should be considered as the standard for care.

6.3.2. Objective and potential benefits of laparoscopic liver surgery in hepatocellular carcinoma

During and after liver resection, blood loss and transfusions are important factors that impact not only early postoperative outcomes but also long-term results with an increased risk of cancer recurrence and decreased patient survival rates (150). However, there is a lack of evidence on the value of LLR for hepatocellular carcinoma (HCC) and severe cirrhosis (138).

The aim of the last studies is to assess the surgical and oncological outcomes of LLR in cirrhotic HCC patients. Liver resections have been shown to be a valuable option for patients with HCC (1). However, the risk of complications as ascitic decompensation, liver failure, bleeding or need for transfusion can be important in patients with severe cirrhosis.

Multiple studies have shown the possibility and validation of the laparoscopic approach in HCC liver resections (63) (151). LLR has been shown to be feasible, safe, and oncologically efficient. However, it has developed slowly in patients with HCC who often suffer from a chronic liver disease which represents an additional challenge for the surgeon.

The experience with large HCCs is even more limited (152). Comparable oncological results have been presented showing several benefits from the point of view of hospital discharge and complications such as ascites and liver failure (55) (62) (67) (110).

Several studies published in the last decade have been of great interest within the multidisciplinary teams, as they suggest that the laparoscopy approach might provide a better tolerance of liver resections in patients with HCC (63) (64). Such results should be considered with caution so far because they had been obtained from retrospective studies with mixed samples.

As time has passed, comparative studies with a larger sample volume in each group and with propensity analysis have been published making a

stronger validation of this approach in patients with liver cirrhosis (58) (61) (62).

Our study shows favorable results for the laparoscopic approach in solitary tumors and minor resections. These results suggest that a laparoscopic approach is similar, if not better than, the open approach for the management of HCC in patients with Child-Pugh A cirrhosis, solitary tumors, and those undergoing minor resections in term of short-term outcomes.

It should be remarked that limited information was available for specific postoperative variables such as mortality (not clearly defined as perioperative, or 30- or 90-days) and PHLF. Henceforth, perioperative mortality was considered as a whole in our analysis.

Similarly, PHLF could not be individually screened by the ISGLS groups and was thus analyzed as a single category. It should be encouraged that all research teams perform statistics for their manuscripts using currently validated classifications rather than institutional or self-raised criteria.

In addition, limited information was available for long-term outcomes of the surgical management of HCC. Only data for 3- and 5-year survival rates provided sufficient detail for analysis. A trend towards improved survival was identified for the laparoscopic approach, however, the data did not reach enough statistical significance.

DFS followed a similar pattern, with the noteworthy exception of an improved rate at 1 year for laparoscopic minor resections. Although statistically significant, this difference should be considered with caution and no strong conclusions should be drawn from this finding as only five studies with a slight dispersion were included in the analysis.

Therefore, the stated objective that the laparoscopic approach can be applied to minimize postoperative complications, transfusion rate, blood loss and others in patients with HCC liver cirrhosis is confirmed. Our review of the literature and meta-analyses shows a growing adoption of laparoscopic liver resection for HCC patients.

Minor resections are now performed by many teams worldwide. Reports of major and complex resections are increasing in the last literature published but remain concentrated in a limited number of expert centres.

For the future, randomized trials are needed and strongly encouraged. Limitations to performing meaningful randomized controlled trials (RCTs) in LLR include variability of procedures (minor, major or atypical resections) and quality underlying liver (fibrosis, cirrhosis, steatosis or normal).

The performance of these studies with correctly stratified and prospective groups will lead to conclusions with greater and more firm statistical evidence with a high diffusion and global acceptance.

Therefore, the laparoscopic approach for HCC liver resections will be disseminated more extensively over a higher number of patients. Training to laparoscopic liver surgery, including the creation of fellowship programs in high-volume units, should be encouraged to improve the safety and quality of patient care (48).

Our results provide a new approach that should be raised in patients diagnosed with potentially resectable HCC. The laparoscopic approach should be considered in HCC liver resection as the first option. Its results confirm the benefits of LLR and promote its expansion to HCC patients with limited liver function.

Current literature is committed to a multimodal approach (138), laparoscopic resection in liver cirrhosis should be considered as a curative option independent of open surgery, due to the benefits it brings to HCC patients.

CONCLUSIONS

1. Our exhaustive literature review, and assessment of current evidence by SIGN methodology has been the basis for the development of the European Guidelines Meeting on Laparoscopic Liver Surgery and for the eachievement of consistent, reliable and evidence-based statements in the application of minimally invasive approaches for the treatment of hepatocellular carcinoma.
2. According to the results of our updated meta-analysis, a minimally invasive approach might be more beneficial compared to an open approach as it may offer a lower rate of complications, blood loss, transfusion rate and postoperative hospital stay for patients with Child-Pugh A cirrhosis, solitary tumors and those undergoing minor resections.
3. Considering severe morbidity including liver-specific posthepatectomy liver failure and 90-days mortality, laparoscopic approach was not different compared to open approach.
4. Laparoscopic approach does not have an impact on short-, mid- and long-term outcomes considering overall survival. A trend towards better disease-free survival when laparoscopic approach is used was observed but no robust conclusions may be obtained. Its impact on re-do hepatectomies or on feasibility of rescue or salvage transplantation procedures remains unresolved.
5. Considering the optimal results obtained from laparoscopic approach, its use for the treatment of hepatocellular carcinoma should be considered as first option and standard of practice in selected patients from high-volume centers in which a multimodal strategy can be offered to these complex patients.

REFERENCES

1. European Association for the Study of the Liver. Electronic address: easloffice@easloffice.eu, European Association for the Study of the Liver. EASL Clinical Practice Guidelines: Management of hepatocellular carcinoma. J Hepatol. 2018 Jul;69(1):182–236.
2. Mak L-Y, Cruz-Ramón V, Chinchilla-López P, Torres HA, LoConte NK, Rice JP, et al. Global Epidemiology, Prevention, and Management of Hepatocellular Carcinoma. Am Soc Clin Oncol Educ Book. 2018 May 23;(38):262–79.
3. Global Burden of Disease Liver Cancer Collaboration, Akinyemiju T, Abera S, Ahmed M, Alam N, Alemayohu MA, et al. The Burden of Primary Liver Cancer and Underlying Etiologies From 1990 to 2015 at the Global, Regional, and National Level: Results From the Global Burden of Disease Study 2015. JAMA Oncol. 2017 Dec 1;3(12):1683–91.
4. Global Cancer Observatory. online. 2019 Jul 14;:1–2.
5. Addissie BD, Roberts LR. Classification and staging of hepatocellular carcinoma: an aid to clinical decision-making. Clin Liver Dis. 2015 May;19(2):277–94.
6. Lu W, Dong J, Huang Z, Guo D, Liu Y, Shi S. Comparison of four current staging systems for Chinese patients with hepatocellular carcinoma undergoing curative resection: Okuda, CLIP, TNM and CUPI. J Gastroenterol Hepatol. 2008 Dec;23(12):1874–8.
7. Okuda K, Ohtsuki T, Obata H, Tomimatsu M, Okazaki N, Hasegawa H, et al. Natural history of hepatocellular carcinoma and prognosis in relation to treatment. Study of 850 patients. Cancer. 1985 Aug 15;56(4):918–28.
8. The Cancer of the Liver Italian Program (Clip) Investigators. A new prognostic system for hepatocellular carcinoma: a retrospective study of 435 patients: the Cancer of the Liver Italian Program (CLIP) investigators. Hepatology. John Wiley & Sons, Ltd; 1998 Sep;28(3):751–5.
9. Kitai S, Kudo M, Minami Y, Ueshima K, Chung H, Hagiwara S, et al. A new prognostic staging system for hepatocellular carcinoma: value of the biomarker combined Japan integrated staging score. Intervirology. 2008;51 Suppl 1:86–94.
10. Llovet JM, Brú C, Bruix J. Prognosis of hepatocellular carcinoma: the BCLC staging classification. Semin Liver Dis. © 1999 by Thieme Medical Publishers, Inc; 1999;19(3):329–38.
11. Santambrogio R, Salceda J, Costa M, Kluger MD, Barabino M, Laurent A, et al. External validation of a simplified BCLC staging system for early hepatocellular carcinoma. Eur J Surg Oncol. 2013 Aug;39(8):850–7.
12. Llovet JM, Burroughs A, Bruix J. Hepatocellular carcinoma. Lancet. 2003 Dec 6;362(9399):1907–17.
13. Forner A, Llovet JM, Bruix J. Hepatocellular carcinoma. Lancet. 2012 Mar 31;379(9822):1245–55.
14. Yau T, Tang VYF, Yao T-J, Fan ST, Lo CM, Poon RTP. Development of Hong Kong Liver Cancer staging system with treatment stratification for patients with hepatocellular carcinoma. Gastroenterology. 2014 Jun;146(7):1691–3.
15. Omata M, Tateishi R, Yoshida H, Shiina S. Treatment of hepatocellular carcinoma by percutaneous tumor ablation methods: Ethanol injection therapy and radiofrequency ablation. Gastroenterology. 2004 Nov;127(5 Suppl 1):S159–66.
16. Mazzaferro V, Battiston C, Perrone S, Pulvirenti A, Regalia E, Romito R, et al. Radiofrequency ablation of small hepatocellular carcinoma in cirrhotic patients awaiting liver transplantation: a prospective study. Annals of Surgery. 2004 Nov;240(5):900–9.
17. Kim Y-S, Lim HK, Rhim H, Lee MW, Choi D, Lee WJ, et al. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors. J Hepatol. 2013 Jan;58(1):89–97.
18. Facciorusso A, Serviddio G, Muscatiello N. Local ablative treatments for hepatocellular carcinoma: An updated review. World J Gastrointest Pharmacol Ther. 2016 Nov

6;7(4):477–89.

19. Chen M-S, Li J-Q, Zheng Y, Guo R-P, Liang H-H, Zhang Y-Q, et al. A prospective randomized trial comparing percutaneous local ablative therapy and partial hepatectomy for small hepatocellular carcinoma. Annals of Surgery. 2006 Mar;243(3):321–8.
20. Huang J, Yan L, Cheng Z, Wu H, Du L, Wang J, et al. A randomized trial comparing radiofrequency ablation and surgical resection for HCC conforming to the Milan criteria. Annals of Surgery. 2010 Dec;252(6):903–12.
21. Feng K, Yan J, Li X, Xia F, Ma K, Wang S, et al. A randomized controlled trial of radiofrequency ablation and surgical resection in the treatment of small hepatocellular carcinoma. J Hepatol. 2012 Oct;57(4):794–802.
22. Fang Y, Chen W, Liang X, Li D, Lou H, Chen R, et al. Comparison of long-term effectiveness and complications of radiofrequency ablation with hepatectomy for small hepatocellular carcinoma. J Gastroenterol Hepatol. 2014 Jan;29(1):193–200.
23. Cho YK, Rhim H, Noh S. Radiofrequency ablation versus surgical resection as primary treatment of hepatocellular carcinoma meeting the Milan criteria: a systematic review. J Gastroenterol Hepatol. 2011 Sep;26(9):1354–60.
24. Wang Y, Luo Q, Li Y, Deng S, Wei S, Li X. Radiofrequency ablation versus hepatic resection for small hepatocellular carcinomas: a meta-analysis of randomized and nonrandomized controlled trials. PLoS ONE. 2014;9(1):e84484.
25. Cucchetti A, Piscaglia F, Cescon M, Colecchia A, Ercolani G, Bolondi L, et al. Cost-effectiveness of hepatic resection versus percutaneous radiofrequency ablation for early hepatocellular carcinoma. J Hepatol. 2013 Aug;59(2):300–7.
26. Raoul J-L, Forner A, Bolondi L, Cheung TT, Kloeckner R, de Baere T. Updated use of TACE for hepatocellular carcinoma treatment: How and when to use it based on clinical evidence. Cancer Treat Rev. 2019 Jan;72:28–36.
27. Facciorusso A, Di Maso M, Muscatiello N. Drug-eluting beads versus conventional chemoembolization for the treatment of unresectable hepatocellular carcinoma: A meta-analysis. Dig Liver Dis. 2016 Jun;48(6):571–7.
28. Ni J-Y, Liu S-S, Xu L-F, Sun H-L, Chen Y-T. Meta-analysis of radiofrequency ablation in combination with transarterial chemoembolization for hepatocellular carcinoma. WJG. 2013 Jun 28;19(24):3872–82.
29. Llovet JM, Zucman-Rossi J, Pikarsky E, Sangro B, Schwartz M, Sherman M, et al. Hepatocellular carcinoma. Nat Rev Dis Primers. 2016 Apr 14;2:16018.
30. Zhong J-H, Ke Y, Gong W-F, Xiang B-D, Ma L, Ye X-P, et al. Hepatic resection associated with good survival for selected patients with intermediate and advanced-stage hepatocellular carcinoma. Annals of Surgery. 2014 Aug;260(2):329–40.
31. Vitale A, Burra P, Frigo AC, Trevisani F, Farinati F, Spolverato G, et al. Survival benefit of liver resection for patients with hepatocellular carcinoma across different Barcelona Clinic Liver Cancer stages: A multicentre study. J Hepatol. European Association for the Study of the Liver; 2015 Mar 1;62(3):617–24.
32. Mazzaferro V, Regalia E, Doci R, Andreola S, Pulvirenti A, Bozzetti F, et al. Liver transplantation for the treatment of small hepatocellular carcinomas in patients with cirrhosis. N Engl J Med. 1996 Mar 14;334(11):693–9.
33. Yao FY, Ferrell L, Bass NM, Watson JJ, Bacchetti P, Venook A, et al. Liver transplantation for hepatocellular carcinoma: expansion of the tumor size limits does not adversely impact survival. Hepatology. 2001 Jun;33(6):1394–403.
34. Roayaie S, Frischer JS, Emre SH, Fishbein TM, Sheiner PA, Sung M, et al. Long-term results with multimodal adjuvant therapy and liver transplantation for the treatment of hepatocellular carcinomas larger than 5 centimeters. Annals of Surgery. 2002 Apr;235(4):533–9.

35. Duffy JP, Vardanian A, Benjamin E, Watson M, Farmer DG, Ghobrial RM, et al. Liver transplantation criteria for hepatocellular carcinoma should be expanded: a 22-year experience with 467 patients at UCLA. Annals of Surgery. 2007 Sep;246(3):502–9–discussion509–11.
36. Volk ML, Vijan S, Marrero JA. A novel model measuring the harm of transplanting hepatocellular carcinoma exceeding Milan criteria. Am J Transplant. 2008 Apr;8(4):839–46.
37. Pavel M-C, Fuster J. Expansion of the hepatocellular carcinoma Milan criteria in liver transplantation: Future directions. WJG. 2018 Aug 28;24(32):3626–36.
38. Vecchio R, MacFayden BV, Palazzo F. History of laparoscopic surgery. Panminerva Med. 2000 Mar;42(1):87–90.
39. Reich H, McGlynn F, DeCaprio J, Budin R. Laparoscopic excision of benign liver lesions. Obstet Gynecol. 1991 Nov;78(5 Pt 2):956–8.
40. Azagra JS, Goergen M, Gilbart E, Jacobs D. Laparoscopic anatomical (hepatic) left lateral segmentectomy-technical aspects. Surgical Endoscopy. 1996 Jul;10(7):758–61.
41. Kaneko H, Takagi S, Shiba T. Laparoscopic partial hepatectomy and left lateral segmentectomy: technique and results of a clinical series. Surgery. 1996 Sep;120(3):468–75.
42. Wakabayashi G. What has changed after the Morioka consensus conference 2014 on laparoscopic liver resection? Hepatobiliary Surg Nutr. 2016 Aug;5(4):281–9.
43. Tanaka S, Kubo S, Kanazawa A, Takeda Y, Hirokawa F, Nitta H, et al. Validation of a Difficulty Scoring System for Laparoscopic Liver Resection: A Multicenter Analysis by the Endoscopic Liver Surgery Study Group in Japan. Journal of the American College of Surgeons. 2017 Aug;225(2):249–258.e1.
44. Kawaguchi Y, Fuks D, Kokudo N, Gayet B. Difficulty of Laparoscopic Liver Resection: Proposal for a New Classification. Annals of Surgery. 2018 Jan;267(1):13–7.
45. Halls MC, Cherqui D, Taylor MA, Primrose JN, Abu Hilal M, Collaborators of The Difficulty of Laparoscopic Liver Surgery Survey. Are the current difficulty scores for laparoscopic liver surgery telling the whole story? An international survey and recommendations for the future. HPB (Oxford). 2018 Mar;20(3):231–6.
46. Belli G, Fantini C, D'Agostino A, Belli A, Russolillo N. Laparoscopic liver resections for hepatocellular carcinoma (HCC) in cirrhotic patients. HPB. 2004 Dec;6(4):236–46.
47. Kaneko H, Takagi S, Otsuka Y, Tsuchiya M, Tamura A, Katagiri T, et al. Laparoscopic liver resection of hepatocellular carcinoma. AJS. 2005 Feb;189(2):190–4.
48. Ciria R, Cherqui D, Geller DA, Briceño J, Wakabayashi G. Comparative Short-term Benefits of Laparoscopic Liver Resection: 9000 Cases and Climbing. Annals of Surgery. 2016 Apr;263(4):761–77.
49. Fretland ÅA, Dagenborg VJ, Bjørnelv GMW, Kazaryan AM, Kristiansen R, Fagerland MW, et al. Laparoscopic Versus Open Resection for Colorectal Liver Metastases: The OSLO-COMET Randomized Controlled Trial. Annals of Surgery. 2018 Feb;267(2):199–207.
50. Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I, et al. The international position on laparoscopic liver surgery: The Louisville Statement, 2008. 2009. pp. 825–30.
51. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han H-S, et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. 2015. pp. 619–29.
52. Abu Hilal M, Aldrighetti L, Dagher I, Edwin B, Troisi RI, Alikhanov R, et al. The Southampton Consensus Guidelines for Laparoscopic Liver Surgery: From Indication to Implementation. Annals of Surgery. 2018 Jul;268(1):11–8.
53. Cherqui D, Laurent A, Tayar C, Chang S, Van Nhieu JT, Loriau JRM, et al. Laparoscopic Liver Resection for Peripheral Hepatocellular Carcinoma in Patients With Chronic Liver Disease. Annals of Surgery. 2006 Apr;243(4):499–506.
54. Santambrogio R, Aldrighetti L, Barabino M,

Pulitanò C, Costa M, Montorsi M, et al. Laparoscopic liver resections for hepatocellular carcinoma. Is it a feasible option for patients with liver cirrhosis? Langenbecks Arch Surg. 2008 Jun 14;394(2):255–64.

55. Aldrighetti L, Guzzetti E, Pulitanò C, Cipriani F, Catena M, Paganelli M, et al. Case-matched analysis of totally laparoscopic versus open liver resection for HCC: short and middle term results. J Surg Oncol. 2010 Jul 1;102(1):82–6.
56. Lai ECH, Tang CN, Ha JPY, Li MKW. Laparoscopic liver resection for hepatocellular carcinoma: ten-year experience in a single center. Arch Surg. American Medical Association; 2009 Feb;144(2):143–7–discussion148.
57. Kim HH, Park EK, Seoung JS, Hur YH, Koh YS, Kim JC, et al. Liver resection for hepatocellular carcinoma: case-matched analysis of laparoscopic versus open resection. J Korean Surg Soc. 2011;80(6):412–8.
58. Kim H, Suh K-S, Lee K-W, Yi N-J, Hong G, Suh S-W, et al. Long-Term Outcome of Laparoscopic Versus Open Liver Resection for Hepatocellular Carcinoma: A Case-Controlled Study with Propensity Score Matching. Surgical Endoscopy. 2013 Oct 23;28(3):950–60.
59. Ahn KS, Kang KJ, Kim YH, Kim T-S, Lim TJ. A Propensity Score-Matched Case-Control Comparative Study of Laparoscopic and Open Liver Resection for Hepatocellular Carcinoma. Journal of Laparoendoscopic & Advanced Surgical Techniques. 2014 Dec;24(12):872–7.
60. Han H-S, Shehta A, Ahn S, Yoon Y-S, Cho JY, Choi Y. Laparoscopic versus open liver resection for hepatocellular carcinoma: Case-matched study with propensity score matching. J Hepatol. 2015 Sep;63(3):643–50.
61. Sposito C, Battiston C, Facciorusso A, Mazzola M, Muscarà C, Scotti M, et al. Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma. British Journal of Surgery. 2016 Jun;103(7):871–80.
62. Takahara T, Wakabayashi G, Beppu T, Aihara A, Hasegawa K, Gotohda N, et al. Long-term and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study. J Hepatobiliary Pancreat Sci. 2015 Jul 1;22(10):721–7.
63. Twaij A. Laparoscopic vsopen approach to resection of hepatocellular carcinoma in patients with known cirrhosis: Systematic review and meta-analysis. WJG. 2014;20(25):8274–9.
64. Kanazawa A, Tsukamoto T, Shimizu S, Kodai S, Yamazoe S, Yamamoto S, et al. Impact of laparoscopic liver resection for hepatocellular carcinoma with F4-liver cirrhosis. Surgical Endoscopy. 2013 Feb 8;27(7):2592–7.
65. Cheung TT, Poon RTP, Yuen WK, Chok KSH, Jenkins CR, Chan SC, et al. Long-Term Survival Analysis of Pure Laparoscopic Versus Open Hepatectomy for Hepatocellular Carcinoma in Patients With Cirrhosis. Annals of Surgery. 2013 Mar;257(3):506–11.
66. Truant S, Bouras AF, Hebbar M, Boleslawski E, Fromont G, Dharancy S, et al. Laparoscopic resection vs. open liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: a case-matched study. Surgical Endoscopy. Springer-Verlag; 2011 Nov;25(11):3668–77.
67. Belli G, Limongelli P, Fantini C, D'Agostino A, Cioffi L, Belli A, et al. Laparoscopic and open treatment of hepatocellular carcinoma in patients with cirrhosis. British Journal of Surgery. 2009 Sep;96(9):1041–8.
68. Chen J, Bai T, Zhang Y, Xie Z-B, Wang X-B, Wu F-X, et al. The safety and efficacy of laparoscopic and open hepatectomy in hepatocellular carcinoma patients with liver cirrhosis: a systematic review. Int J Clin Exp Med. 2015;8(11):20679–89.
69. Memeo R, de'Angelis N, Compagnon P, Salloum C, Cherqui D, Laurent A, et al. Laparoscopic vs. Open Liver Resection for Hepatocellular Carcinoma of Cirrhotic Liver: A Case–Control Study. World Journal of Surgery. 2014 Jun 10;38(11):2919–26.

70. Siniscalchi A, Ercolani G, Tarozzi G, Gamberini L, Cipolat L, Pinna AD, et al. Laparoscopic versus Open Liver Resection: Differences in Intraoperative and Early Postoperative Outcome among Cirrhotic Patients with Hepatocellular Carcinoma-A Retrospective Observational Study. HPB Surg. Hindawi; 2014;2014:871251–7.
71. PhD Y-IYM, PhD TIM, MD TK, MD YY, PhD KTM, PhD SIM, et al. Long-Term Favorable Surgical Results of Laparoscopic Hepatic Resection for Hepatocellular Carcinoma in Patients with Cirrhosis: A Single-Center Experience over a 10-Year Period. Journal of the American College of Surgeons. American College of Surgeons; 2014 Dec 1;219(6):1117–23.
72. Morise Z, Ciria R, Cherqui D, Chen K-H, Belli G, Wakabayashi G. Can we expand the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. J Hepatobiliary Pancreat Sci. 2015 May;22(5):342–52.
73. Belghiti J, Kianmanesh R. Surgical treatment of hepatocellular carcinoma. HPB (Oxford). 2005;7(1):42–9.
74. Makuuchi M. Surgical treatment for HCC--special reference to anatomical resection. Int J Surg. 2013;11 Suppl 1:S47–9.
75. Takasaki K. Glissonean pedicle transection method for hepatic resection: a new concept of liver segmentation. J Hepatobiliary Pancreat Surg. 1998;5(3):286–91.
76. Wakai T, Shirai Y, Sakata J, Kaneko K, Cruz PV, Akazawa K, et al. Anatomic resection independently improves long-term survival in patients with T1-T2 hepatocellular carcinoma. Ann Surg Oncol. 6 ed. Springer-Verlag; 2007 Apr;14(4):1356–65.
77. Fasel JHD, Schenk A. Concepts for Liver Segment Classification: Neither Old Ones nor New Ones, but a Comprehensive One. J Clin Imaging Sci. 2013 Oct 29;3:48.
78. Kang KJ, Ahn KS. Anatomical resection of hepatocellular carcinoma: A critical review of the procedure and its benefits on survival. WJG. 2017 Feb 21;23(7):1139–46.
79. Xiao L, Xiang L-J, Li J-W, Chen J, Fan Y-D, Zheng S-G. Laparoscopic versus open liver resection for hepatocellular carcinoma in posterosuperior segments. Surgical Endoscopy. Springer US; 2015 Oct;29(10):2994–3001.
80. Komatsu S, Brustia R, Goumard C, Perdigao F, Soubrane O, Scatton O. Laparoscopic versus open major hepatectomy for hepatocellular carcinoma: a matched pair analysis. Surgical Endoscopy. 7 ed. Springer US; 2016 May;30(5):1965–74.
81. Zhang Y, Huang J, Chen X-M, Sun D-L. A Comparison of Laparoscopic Versus Open Left Hemihepatectomy for Hepatocellular Carcinoma. Surg Laparosc Endosc Percutan Tech. 2016 Apr;26(2):146–9.
82. Lee JJ, Conneely JB, Smoot RL, Gallinger S, Greig PD, Moulton C-A, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma at a North-American Centre: a 2-to-1 matched pair analysis. HPB. 2015 Apr;17(4):304–10.
83. Cho JY, Han H-S, Yoon Y-S, Choi Y, Lee W. Outcomes of laparoscopic right posterior sectionectomy in patients with hepatocellular carcinoma in the era of laparoscopic surgery. Surgery. 2015 Jul;158(1):135–41.
84. Ciria R, Gomez-Luque I, Ocaña S, Cipriani F, Halls M, Briceño J, et al. A Systematic Review and Meta-Analysis Comparing the Short- and Long-Term Outcomes for Laparoscopic and Open Liver Resections for Hepatocellular Carcinoma: Updated Results from the European Guidelines Meeting on Laparoscopic Liver Surgery, Southampton, UK, 2017. Ann Surg Oncol. Springer International Publishing; 2018 Nov 2;365(12):1118–12.
85. Beller EM, Glasziou PP, Altman DG, Hopewell S, Bastian H, Chalmers I, et al. PRISMA for Abstracts: reporting systematic reviews in journal and conference abstracts. 2013. p. e1001419.
86. Harbour R, Lowe G, Twaddle S. Scottish Intercollegiate Guidelines Network: the first

15 years (1993-2008). J R Coll Physicians Edinb. 2011 Jun;41(2):163–8.

87. Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, et al. Evaluating non-randomised intervention studies. Health Technol Assess. 2003;7(27):iii–x–1–173.
88. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials. 1986 Sep;7(3):177–88.
89. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ. British Medical Journal Publishing Group; 2003 Sep 6;327(7414):557–60.
90. Fleiss JL. The statistical basis of meta-analysis. Stat Methods Med Res. 1993;2(2):121–45.
91. Hoffman JIE. Biostatistics for Medical and Biomedical Practitioners. Academic Press; 2015. 1 p.
92. MANTEL N, HAENSZEL W. Statistical aspects of the analysis of data from retrospective studies of disease. J Natl Cancer Inst. 1959 Apr;22(4):719–48.
93. Journal of statistical software. Alexandria, VA: American Statistical Association.
94. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. arXiv.org. 2014. p. arXiv:1407.8038.
95. Lee KF, Chong CN, Wong J, Cheung YS, Wong J, Lai P. Long-Term Results of Laparoscopic Hepatectomy Versus Open Hepatectomy for Hepatocellular Carcinoma: A Case-Matched Analysis. World Journal of Surgery. 2011 Aug 13;35(10):2268–74.
96. Hu B-S. Comparison of laparoscopic vsopen liver lobectomy (segmentectomy) for hepatocellular carcinoma. WJG. 2011;17(42):4725–4.
97. Ker CG, Chen JS, Kuo KK, Chuang SC, Wang SJ, Chang WC, et al. Liver Surgery for Hepatocellular Carcinoma: Laparoscopic versus Open Approach. International Journal of Hepatology. 2011;2011(1):1–6.
98. Endo Y, Ohta M, Sasaki A, Kai S, Eguchi H, Iwaki K, et al. A comparative study of the long-term outcomes after laparoscopy-assisted and open left lateral hepatectomy for hepatocellular carcinoma. Surg Laparosc Endosc Percutan Tech. 2009 Oct;19(5):e171–4.
99. Laurent A, Cherqui D, Lesurtel M, Brunetti F, Tayar C, Fagniez P-L. Laparoscopic liver resection for subcapsular hepatocellular carcinoma complicating chronic liver disease. Arch Surg. American Medical Association; 2003 Jul;138(7):763–9–discussion769.
100. Zhang J, Zhou Z-G, Huang Z-X, Yang K-L, Chen J-C, Chen J-B, et al. Prospective, single-center cohort study analyzing the efficacy of complete laparoscopic resection on recurrent hepatocellular carcinoma. Chin J Cancer. BioMed Central; 2016 Mar 8;35(1):25.
101. Luo L, Zou H, Yao Y, Huang X. Laparoscopic versus open hepatectomy for hepatocellular carcinoma: short- and long-term outcomes comparison. Int J Clin Exp Med. 2015;8(10):18772–8.
102. Beppu T, Hayashi H, Okabe H, Imai K, Nitta H, Masuda T, et al. Hybrid-including endoscopic versus open hepatic resection for patients with hepatocellular carcinoma meeting the Milan criteria: a propensity case-matched analysis. Anticancer Res. 2015 Mar;35(3):1583–90.
103. Cheung TT, Poon RTP, Dai WC, Chok KSH, Chan SC, Lo CM. Pure Laparoscopic Versus Open Left Lateral Sectionectomy for Hepatocellular Carcinoma: A Single-Center Experience. World Journal of Surgery. 2016 Jan;40(1):198–205.
104. Kobayashi S, Nagano H, Marubashi S, Kawamoto K, Wada H, Eguchi H, et al. Hepatectomy based on the tumor hemodynamics for hepatocellular carcinoma: a comparison among the hybrid and pure laparoscopic procedures and open surgery. Surgical Endoscopy. 2012 Aug 31;27(2):610–7.
105. Belli G, Fantini C, D'Agostino A, Cioffi L, Langella S, Russolillo N, et al. Laparoscopic versus open liver resection for hepatocellular carcinoma in patients with histologically proven cirrhosis: short- and middle-term results. Surgical Endoscopy. 2007

Nov;21(11):2004–11.
106. Shimada M, Hashizume M, Maehara S, Tsujita E, Rikimaru T, Yamashita Y, et al. Laparoscopic hepatectomy for hepatocellular carcinoma. Surgical Endoscopy. 2014 Apr 19;15(6):541–4.
107. Kim S-J, Jung H-K, Lee D-S, Yun S-S, Kim H-J. The comparison of oncologic and clinical outcomes of laparoscopic liver resection for hepatocellular carcinoma. Ann Surg Treat Res. 2014;86(2):61–7.
108. Ai J-H, Li J-W, Chen J, Bie P, Wang S-G, Zheng S-G. Feasibility and safety of laparoscopic liver resection for hepatocellular carcinoma with a tumor size of 5-10 cm. PLoS ONE. 2013;8(8):e72328.
109. Nguyen KT. Comparative Benefits of Laparoscopic vs Open Hepatic Resection. Arch Surg. 2011 Mar 1;146(3):348–9.
110. Tranchart H, Di Giuro G, Lainas P, Roudie J, Agostini H, Franco D, et al. Laparoscopic resection for hepatocellular carcinoma: a matched-pair comparative study. Surgical Endoscopy. 2009 Nov 14;24(5):1170–6.
111. Ito T, Tanaka S, Iwai S, Takemura S, Hagihara A, Uchida-Kobayashi S, et al. Outcomes of laparoscopic hepatic resection versus percutaneous radiofrequency ablation for hepatocellular carcinoma located at the liver surface: A case-control study with propensity score matching. Hepatol Res. 2016 May;46(6):565–74.
112. Xiang L, Xiao L, Li J, Chen J, Fan Y, Zheng S. Safety and Feasibility of Laparoscopic Hepatectomy for Hepatocellular Carcinoma in the Posterosuperior Liver Segments. World Journal of Surgery. 2015 Jan 14;39(5):1202–9.
113. Leong WQ. Comparative study and systematic review of laparoscopic liver resection for hepatocellular carcinoma. WJH. 2015;7(27):2765–10.
114. Shehta A, Han H-S, Yoon Y-S, Cho JY, Choi Y. Laparoscopic liver resection for hepatocellular carcinoma in cirrhotic patients: 10-year single-center experience. Surgical Endoscopy. Springer US; 2016 Feb;30(2):638–48.
115. Xiong J-J, Altaf K, Javed MA, Huang W, Mukherjee R, Mai G, et al. Meta-analysis of laparoscopic vs open liver resection for hepatocellular carcinoma. WJG. 2012 Dec 7;18(45):6657–68.
116. Yoon Y-I, Kim K-H, Kang S-H, Kim W-J, Shin M-H, Lee S-K, et al. Pure Laparoscopic Versus Open Right Hepatectomy for Hepatocellular Carcinoma in Patients With Cirrhosis: A Propensity Score Matched Analysis. Annals of Surgery. 2017 May;265(5):856–63.
117. Yoon Y-S, Han H-S, Cho JY, Ahn KS. Total laparoscopic liver resection for hepatocellular carcinoma located in all segments of the liver. Surgical Endoscopy. 2009 Dec 25;24(7):1630–7.
118. Dua MM, Worhunsky DJ, Hwa K, Poultsides GA, Norton JA, Visser BC. Extracorporeal Pringle for laparoscopic liver resection. Surgical Endoscopy. Springer US; 2015 Jun;29(6):1348–55.
119. Zhen ZJ, Lau WY, Wang FJ, Lai ECH. Laparoscopic liver resection for hepatocellular carcinoma in the left liver: Pringle maneuver versus tourniquet method. World Journal of Surgery. 2010 Feb;34(2):314–9.
120. Harada N, Maeda T, Yoshizumi T, Ikeda T, Kayashima H, Ikegami T, et al. Laparoscopic Liver Resection Is a Feasible Treatment for Patients with Hepatocellular Carcinoma and Portal Hypertension. Anticancer Res. 2016 Jul;36(7):3489–97.
121. Cai X, Liang X, Yu T, Liang Y, Jing R, Jiang W, et al. Liver cirrhosis grading Child-Pugh class B: a Goliath to challenge in laparoscopic liver resection?-prior experience and matched comparisons. Hepatobiliary Surg Nutr. 2015 Dec;4(6):391–7.
122. Takahara T, Wakabayashi G, Nitta H, Hasegawa Y, Katagiri H, Takeda D, et al. Laparoscopic liver resection for hepatocellular carcinoma with cirrhosis in a single institution. Hepatobiliary Surg Nutr. 2015 Dec;4(6):398–405.
123. Morise Z, Sugioka A, Kawabe N, Umemoto S, Nagata H, Ohshima H, et al. Pure laparoscopic hepatectomy for hepatocellular carcinoma patients with severe liver cirrhosis. Asian J Endosc Surg. 2011 Aug;4(3):143–6.

124. Vitali GC, Laurent A, Terraz S, Majno P, Buchs NC, Rubbia-Brandt L, et al. Minimally invasive surgery versus percutaneous radio frequency ablation for the treatment of single small (≤3 cm) hepatocellular carcinoma: a case-control study. Surgical Endoscopy. Springer US; 2016 Jun;30(6):2301–7.
125. Lai C, Jin R-A, Liang X, Cai X-J. Comparison of laparoscopic hepatectomy, percutaneous radiofrequency ablation and open hepatectomy in the treatment of small hepatocellular carcinoma. J Zhejiang Univ Sci B. 2016 Mar;17(3):236–46.
126. Baloyiannis I, Perivoliotis K, Ntellas P, Dadouli K, Tzovaras G. Comparing the safety, efficacy, and oncological outcomes of laparoscopic and open colectomy in transverse colon cancer: a meta-analysis. Int J Colorectal Dis. Springer Berlin Heidelberg; 2020 Mar;35(3):373–86.
127. Jensen KK, Nordholm-Carstensen A, Krarup P-M, Jorgensen LN. Incidence of Incisional Hernia Repair After Laparoscopic Compared to Open Resection of Colonic Cancer: A Nationwide Analysis of 17,717 Patients. World Journal of Surgery. Springer International Publishing; 2020 Jan 10;146:594–10.
128. Kethman WC, Harris AHS, Morris AM, Shelton A, Kirilcuk N, Kin C. Oncologic and Perioperative Outcomes of Laparoscopic, Open, and Robotic Approaches for Rectal Cancer Resection: A Multicenter, Propensity Score-Weighted Cohort Study. Dis Colon Rectum. 2020 Jan;63(1):46–52.
129. Shin JK, Kim HC, Lee WY, Yun SH, Cho YB, Huh JW, et al. Comparative study of laparoscopic versus open technique for simultaneous resection of colorectal cancer and liver metastases with propensity score analysis. Surgical Endoscopy. Springer US; 2019 Nov 15;14(3):195–9.
130. Syn NL, Kabir T, Koh YX, Tan HL, Wang LZ, Chin BZ, et al. Survival Advantage of Laparoscopic Versus Open Resection For Colorectal Liver Metastases: A Meta-analysis of Individual Patient Data From Randomized Trials and Propensity-score Matched Studies. Annals of Surgery. 2019 Oct 22.
131. Tianci C, Shen Z, Chen S, Lin Y, Gao L, Zhang Z, et al. Median sternotomy versus minimally invasive thymectomy for early-stage thymoma: A systematic review and meta-analysis protocol. Medicine. 2019 Dec;98(51):e18359.
132. Kneuertz PJ, D'Souza DM, Richardson M, Abdel-Rasoul M, Moffatt-Bruce SD, Merritt RE. Long-Term Oncologic Outcomes After Robotic Lobectomy for Early-stage Non-Small-cell Lung Cancer Versus Video-assisted Thoracoscopic and Open Thoracotomy Approach. Clin Lung Cancer. 2019 Oct 13.
133. Scaletta G, Dinoi G, Capozzi V, Cianci S, Pelligra S, Ergasti R, et al. Comparison of minimally invasive surgery with laparotomic approach in the treatment of high risk endometrial cancer: A systematic review. Eur J Surg Oncol. 2019 Dec 2.
134. Capozzi VA, Sozzi G, Gambino G, Cianciolo A, Riccò M, Monfardini L, et al. Laparoscopy versus laparotomy for surgical treatment of obese women with endometrial cancer: A cost-benefit comparative analysis. Mol Clin Oncol. 2019 Oct;11(4):335–42.
135. Hilal MA. Why do we need guidelines in laparoscopic liver surgery? HPB (Oxford). Elsevier Ltd; 2017 Apr 1;19(4):287–8.
136. Zhou Y-M, Shao W-Y, Zhao Y-F, Xu D-H, Li B. Meta-analysis of laparoscopic versus open resection for hepatocellular carcinoma. Dig Dis Sci. 2011 Jul;56(7):1937–43.
137. Fancellu A, Rosman AS, Sanna V, Nigri GR, Zorcolo L, Pisano M, et al. Meta-analysis of trials comparing minimally-invasive and open liver resections for hepatocellular carcinoma. J Surg Res. 2011 Nov;171(1):e33–45.
138. Cipriani F, Fantini C, Ratti F, Lauro R, Tranchart H, Halls M, et al. Laparoscopic liver resections for hepatocellular carcinoma. Can we extend the surgical indication in cirrhotic patients? Surgical Endoscopy. Springer US; 2018 Feb;32(2):617–26.
139. Evidence-Based Medicine Working Group. Evidence-based medicine. A new approach to teaching the practice of medicine. JAMA. 1992 Nov 4;268(17):2420–5.

140. Metzdorff MT. Evidence-based medicine: what it is, what it isn't, and are we practicing it? J Trauma Acute Care Surg. 2013 Dec;75(6):927–35.
141 Kicinski M. Publication bias in recent meta-analyses. PLoS ONE. 2013;8(11):e81823–.
142. Egger M, Smith GD. Bias in location and selection of studies. BMJ. 1998 Jan 3;316(7124):61–6.
143. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. Statistics in Medicine 2002;21:1539-1558.
144. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. British Medical Journal 2003;327:557-560.
145. Hedges LV, Pigott TD. The power of statistical tests in meta-analysis, Psychological Methods 2001;6:203-217.
146. Fleiss JL, Gross AJ. Meta-analysis in epidemiology, with special reference to studies of the association between exposure to environmental tobacco smoke and lung cancer: A critique. Journal of Clinical Epidemiology 1991;44:127-39.
147. Ades AE, Higgins JPT. The Interpretation of Random-Effects Meta-Analysis in Decision Models. Medical Decision Making 2005;25:646-654.
148. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. BMC Med Res Methodol. 5 ed. 2005 Apr 20;5(1):xi, 564–10.
149. Wan X, Wang W, Liu J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. BMC Med Res Methodol. BioMed Central; 2014 Dec 19;14(1):135–13.
150. Bossola M, Pacelli F, Bellantone R, Doglietto GB. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. Annals of Surgery. 2005 Feb;241(2):381.
151. McPhail MJW, Scibelli T, Abdelaziz M, Titi A, Pearce NW, Abu Hilal M. Laparoscopic versus open left lateral hepatectomy. Expert Rev Gastroenterol Hepatol. 2009 Aug;3(4):345–51.
152. Levi Sandri GB, Spoletini G, Vennarecci G, Francone E, Abu Hilal M, Ettorre GM. Laparoscopic liver resection for large HCC: short- and long-term outcomes in relation to tumor size. Surgical Endoscopy. 2018 Dec;32(12):4772–9.)

ASSOCIATED PUBLICATIONS

- Abu Hilal M, Aldrighetti L, Dagher I, Edwin B, Troisi RI, Alikhanov R, Aroori S, Belli G, Besselink M, Briceno J, Gayet B, D' Hondt M, Lesurtel M, Menon K, Lodge P, Rotellar F, Santoyo J, Scatton O, Soubrane O, Sutcliffe R, Van Dam R, White S, Halls MC, Cipriani F, Van der Poel M, Ciria R, Barhatov L, **Gomez-Luque I**, Ocana-Garcia S, Cook A, Buell J, Clavien PA, Dervenis C, Fusai G, Geller D, Lang H, Primrose J, Taylor M, Van Gulik T, Wakabayashi G, Asbun H, Cherqui D. The Southampton Consensus Guidelines for Laparoscopic Liver Surgery: From Indication to Implementation. Annals of Surgery. 2018 Jul;268(1):11–8.
- Ciria R, **Gomez-Luque I**, Ocaña S, Cipriani F, Halls M, Briceño J, et al. A Systematic Review and Meta-Analysis Comparing the Short- and Long-Term Outcomes for Laparoscopic and Open Liver Resections for Hepatocellular Carcinoma: Updated Results from the European Guidelines Meeting on Laparoscopic Liver Surgery, Southampton, UK, 2017. Ann Surg Oncol. Springer International Publishing; 2018 Nov 2;365(12):1118–12.

ORIGINAL ARTICLE

The Southampton Consensus Guidelines for Laparoscopic Liver Surgery

From Indication to Implementation

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Objective: The European Guidelines Meeting on Laparoscopic Liver Surgery was held in Southampton on February 10 and 11, 2017 with the aim of presenting and validating clinical practice guidelines for laparoscopic liver surgery.

Background: The exponential growth of laparoscopic liver surgery in recent years mandates the development of clinical practice guidelines to direct the speciality's continued safe progression and dissemination.

Methods: A unique approach to the development of clinical guidelines was adopted. Three well-validated methods were integrated: the Scottish Intercollegiate Guidelines Network methodology for the assessment of evidence and development of guideline statements; the Delphi method of establishing expert consensus, and the AGREE II-GRS Instrument for the assessment of the methodological quality and external validation of the final statements.

Results: Along with the committee chairman, 22 European experts; 7 junior experts and an independent validation committee of 11 international surgeons produced 67 guideline statements for the safe progression and dissemination of laparoscopic liver surgery. Each of the statements reached at least a 95% consensus among the experts and were endorsed by the independent validation committee.

Conclusion: The European Guidelines Meeting for Laparoscopic Liver Surgery has produced a set of clinical practice guidelines that have been independently validated for the safe development and progression of laparoscopic liver surgery. The Southampton Guidelines have amalgamated the available evidence and a wealth of experts' knowledge taking in consideration the relevant stakeholders' opinions and complying with the international methodology standards.

Keywords: clinical practice, consensus, guidelines, implementation, indication, laparoscopic liver surgery, patient selection, procedures, Southampton, technique

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The first European Guidelines Meeting on Laparoscopic Liver Surgery (EGMLLS) was held in Southampton on February 10 and 11, 2017, with the specific aim of presenting and validating guidelines for laparoscopic liver surgery (LLS).

Previously, the consensus meeting in Louisville (2008)[1] reviewed the feasibility of LLS, whereas that of Morioka (2014)[2] focused on a comparison with open resections, then the current standard of practice, demonstrating a clear role for the laparoscopic approach in the modern era of liver surgery. While the laparoscopic approach must continue to demonstrate a lack of inferiority compared with the open approach, the future must be directed at its potential advantages, development, and safe progression.[3] Building on the foundation laid by the 2 previous meetings, this manuscript represents clinical practice guidelines designed specifically to direct the safe future development of laparoscopic liver surgery. The Southampton Guidelines aim to provide both experienced and training surgeons, and centers, guidance as to the appropriateness of care, to reduce variations in practice and to facilitate the safe expansion of LLS with the goal of improving patient care.[4]

METHODS

The members of the steering committee and the expert panel were selected by the committee chairman for their wealth of experience and their significant contributions to the development of laparoscopic liver surgery. Of the 11 members of the international validation committee, 7 surgeons only perform open resections, whereas the remaining 4 surgeons perform both open and laparoscopic liver surgery. To provide clear clinical practice guidelines on LLS and its safe expansion, 5 key domains were identified by the Steering Committee: Indications, Patient selection, Procedures, Techniques, and Implementation. Each domain was further subdivided into topics, for example, the "*Indication*" domain was separated into: resections for "*Colorectal Liver Metastases*," "*Hepatocellular Carcinoma*," and "*Benign and Other Rare Liver Metastases*." In addition to the 5 members of the steering committee, a further 18 liver surgeons, all with recognized expertise in LLS, were selected to form the Expert Panel. The expert panel was divided into working groups, and each was assigned a number of topics to develop specific guidelines. An independent validation committee of 11 experts and 2 patient representatives was involved throughout the process of statement production.

The methodology for the production of the Southampton Guidelines was developed in collaboration with an independent methodologist. A unique approach to the production was adopted by integrating 3 validated methods: the SIGN (Scottish Intercollegiate Guidelines Network) methodology for the assessment of evidence and development of guideline statements[5]; the Delphi method (for establishing expert consensus)[6]; and the AGREE II-GRS (Global Rating Scale) Instrument[7] for the assessment of the methodological quality and external validation of the final statements.

A systematic review using Ovid Medline and Pubmed was undertaken in July 2016 and repeated in January 2017 to review all the existing literature for each topic. All manuscripts meeting the inclusion criteria were evaluated using the SIGN methodology to establish the Study Quality and assigned an Evidence Level (supplementary Appendix S1; http://links.lww.com/SLA/B340 and Fig. 1; Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram). Through the use of Considered Judgement Forms (as per the SIGN methodology), the findings of the systematic review and the opinions of the experts in each working group were combined to form the provisional statements. A form of recommendation (ie, strength), based upon the level of evidence from the systematic review, was assigned to each statement (supplementary Appendix S2; http://links.lww.com/SLA/B340). All the statements were amalgamated and disseminated to the entire expert panel for voting in accordance with the Delphi methodology. This methodology allows each expert to either agree or disagree with a given statement, and make recommendations for changes to that statement should they feel it necessary. If a statement reached greater than or equal to a 95% agreement in the first Delphi round, it was accepted

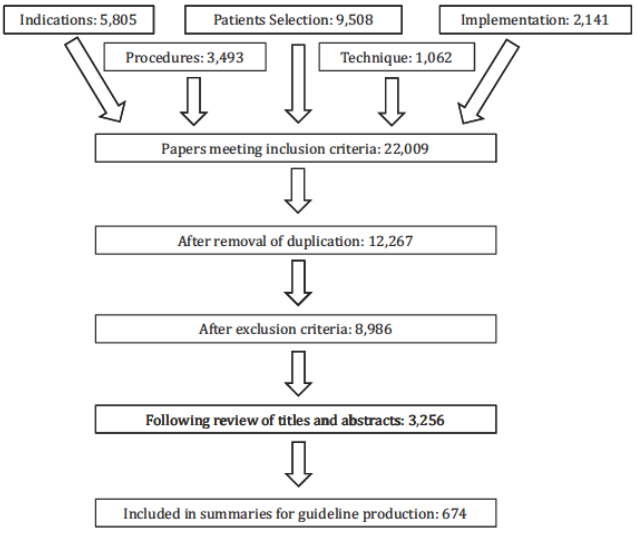

FIGURE 1. PRISMA diagram. A graphical representation of the included publications within the systematic review. Searches were performed in July 2016 and repeated in January 2017 using OVID Medline and Pubmed searches. Inclusion criteria: any publication relating to laparoscopic liver surgery; exclusion criteria: nonhuman studies, comparative studies with less than 10 cases, case reports, non-English and full-text unavailable. Each search contains: [Laparosco* OR minimally-invasive OR Keyhole] AND [Liver OR Hepat* OR Liver Surgery OR Liver Resection], With the addition of searches specific to topic for example in "Bleeding": AND [blood OR bleeding OR haemorrhage OR Haemosta*].

into the guidelines for presentation at the meeting and removed from further Delphi rounds. Statements failing to reach a 95% agreement were returned to the original working group, along with their respective anonymized comments, for revision, and were entered into the subsequent Delphi round. After 3 Delphi rounds, 66 statements had reached at least a 95% agreement and 3 had not. The identities of those producing the provisional statements and those providing feedback remained anonymous except to the guideline's chairman.

At the pre-meeting assembly, a fourth Delphi round was held with the intent to review the guideline statements and reach a consensus on the 3 outstanding statements. In addition, the form of recommendations assigned to each statement was reviewed, assessed, and modified to ensure the evidence level provided neither over nor under-represented the statement. This was performed taking into consideration factors such as the clinical importance of the topic, the relevance of implications to the clinical setting, and the consistency of the body of evidence. At this point, 2 statements were removed as they failed to reach agreement; hence 67 statements were accepted for the meeting. The Validation Committee reviewed the literature searches and the subsequent summaries used for the production of the guideline statements, specifically examining the methodological techniques underpinning the production of each statement as per the AGREE II-GRS tool.[8]

In addition to the expert panel and validation committee, the 2-day conference was attended by over 190 specialists, from 23 different countries, all sharing an interest in liver surgery. During the conference, the highest-level evidence supporting each statement was presented along with the form of recommendation. In addition, all in attendance voted electronically, demonstrating their additional support, or otherwise, for each statement. The validation committee considered the outcomes of these votes, the opinions of the patient representatives, and proposed a number of recommendations before granting endorsement. The expert panel accepted all the recommendations from the validation committee. A detailed description of this novel methodology for the development of surgical guidelines will be published separately, as will the detailed systematic reviews for the core topics.

GUIDELINES

The Southampton Guidelines were derived from the aforementioned methodology and thus are based on published evidence and expert opinion. It is of critical importance to note that the majority of the evidence originates from surgeons experienced in both liver surgery and advanced laparoscopic techniques working in specialist liver centers. Therefore, the guidelines should not be misconstrued as an endorsement for surgeons to perform LLS without the necessary experience and training or in an institution without the proficiency and support to practice liver surgery. It is also noteworthy that LLS accounts for 30% to 60% of liver resections in these specialist centers, and therefore there are implicit selection criteria to assess which patients are deemed appropriate candidates for a laparoscopic approach. The criteria vary among institutions and surgeons in accordance with proficiency and expertise; and will evolve with time.

Section 1: Indications

Topic 1: Colorectal Liver Metastases (CRLM)

Are Laparoscopic Liver Resections (LLR) Indicated for the Management of CRLM? The literature suggests improved short-term outcomes for LLR of CRLM compared with open liver resection (OLR) with similar long-term outcomes. A recent meta-analysis found a reduced blood loss and need for transfusion with comparable operative times and length of hospital stay in the laparoscopic group. Overall survival and disease-free survival were similar between the groups, and a lower incidence of R1 resections was observed in the laparoscopic group.[9] Preliminary results from the first large-scale prospective randomized control trial (COMET)[10] comparing laparoscopic and OLRs for CRLM have shown improved short-term outcomes for the laparoscopic approach, which is supported by previous propensity score-matched studies.[11] Other studies report similar benefits in those aged over 70.[12] Increasing margin width in R0 resections did not significantly correlate with better overall survival,[13] and as such, the guidelines confirm that parenchymal sparing resections should continue to be the basis of treatment of CRLM. The guidelines conclude that with appropriate expertise, the laparoscopic approach is a valid alternative to the treatment of CRLM (R1.1 and R1.2; see supplementary Table S1; http://links.lww.com/SLA/B340 for complete list of recommendations.

What is the Role of Laparoscopy in the Management of Simultaneous Colonic and Liver Resection for Synchronous Colorectal Metastases? A laparoscopic approach was associated with a shorter hospital stay than an open approach with no difference in overall survival for patients with synchronous hepatectomy and colectomy.[14] There is, however, insufficient comparative data for combined major liver and colorectal resections. The experts agreed that combined laparoscopic major liver and colonic resections are complex and lengthy procedures with the potential for increased operative risks. However, simultaneous resections for nonrectal primaries with peripheral liver lesions requiring limited hepatectomy or left lateral sectionectomy were considered a good treatment option. Systematic review suggests that the timing of liver resection for synchronous liver metastasis should be decided according to technical and oncological considerations.[15] The guidelines emphasize a need for a multidisciplinary approach to these patients (see R2.2, R2.2, and R2.3).

Topic 2: Benign and Rare Noncolorectal Metastases

What is the Role of LLR in the Management of Benign Disease and Rare Noncolorectal Metastases? Operative trends for benign disease demonstrate that the proportion of cases performed laparoscopically is increasing.[16] LLR for benign lesions has lower intraoperative blood loss, frequency of complications, postoperative analgesic requirements, time to oral intake, and a shorter hospital stay.[17] With respect to neuroendocrine tumors (NETs), observational studies[18] highlight the feasibility, safety, and oncological efficiency of LLR for NETs and other noncolorectal liver metastasis when clinically indicated (see R3.1 and R3.2).

Topic 3: Hepatocellular Carcinoma (HCC)

Is LLR Indicated for the Management of HCC? Meta-analysis and large propensity score-matched studies of open versus laparoscopic liver resection for HCC have strongly suggested that LLR for HCC is associated with reduced blood loss, transfusion rate, postoperative ascites, and liver failure and hospital stay with comparable operation time, disease-free margin, and recurrence rates.[19,20] This has been confirmed for major resections in a recent series.[21] For minor resections, a laparoscopic approach was found to be the only independent factor to reduce the complication rate in resections for HCC[22] (see R4.1, R4.2, R4.3, and R4.4).

What is the Role of LLR in Cirrhotic Patients? No differences in operative time, blood loss, intraoperative complications, hospital stay, and morbidity were found in LLR for cirrhotics compared with noncirrhotics.[23] A laparoscopic approach appears to reduce the incidence of postoperative ascites, liver failure,[24] and morbidity assessed in terms of "Comprehensive Complication Index," with no difference in overall or disease-free survival at 2 years.[25] The

evidence for both LLR in patients with significant portal hypertension, ascites, and Child-Pugh B cirrhosis is limited to single studies,[26,27] and as such the guidelines recommend caution with these patient cohorts (see R5.1, R5.2, and R5.3).

Topic 4: Living Donor

What is the Role of the Laparoscopic Technique for Living Donor Hepatectomy (LDH)? The evidence suggests that there is an improved quality of life with LLS for LDH that includes a shorter hospital stay and an earlier return to work.[28] The experts discussed the differences between left lateral graft retrieval for pediatric transplantation and full right or full left hepatectomy for adult transplantation. It was highlighted that the evidence for full right and full left hepatectomy is primarily based on laparoscopic-assisted procedures (hybrid) with only limited studies focusing on pure laparoscopic donor hepatectomy and hence minimally invasive donor major hepatectomy has not yet been standardized and should be restricted to expert centers (see R6.1, R6.2, R6.3, and R6.4).

Section 2: Patients and Complex Diseases

Topic 5: High-risk Patients

Are There Contraindications for LLR in Elderly and High Body Mass Index (BMI) Patients (Fragile Patients)? Laparoscopic liver resection for elderly patients has demonstrated lower intraoperative blood loss, hospital stay, and morbidity, with comparable oncological outcomes to OLR.[12,29] There are limited comparative studies regarding LLR in obese patients, but evidence suggests that in selected patients, it is an appropriate treatment strategy[30] (see R7.1, R7.2, and R7.3).

Topic 6: Redo Liver Resections

Are LLRs Feasible in Patients With Previous Liver Resection? Evidence suggests that LLR for re-do liver surgery is an appropriate option, although repeat resections have greater operative time and blood loss than primary resections.[31,32] The experts suggested that an initial laparoscopic resection may facilitate repeated resections by limiting the amount of adhesions, thereby providing an important advantage (see R8).

Topic 7: Technically Complex Settings

Is There a Role for LLR in Patients Requiring 2-Stage Hepatectomy? There are limited comparative studies specifically regarding LLR for 2-stage hepatectomies. Observational studies suggests it is feasible and without detrimental effects on long-term outcomes[33,34] (see R9).

Is LLR Feasible in Patients With Large Lesions and Lesions in Close Proximity to Major Vessels? Reports from cohorts studies of large (5–10 cm) and giant (>10 cm) tumors suggest that the resection of such lesions can be addressed laparoscopically with no increased morbidity. However, greater operative time and blood loss was observed when compared with LLS for smaller tumors.[35,36] Other reports have shown that in expert hands, lesions located in close proximity to the major vasculature can be addressed laparoscopically without detrimental effects[37] (see R10.1 and R10.2).

Section 3: Procedures

Topic 8: Major Hepatectomies

What is the Role of the Laparoscopic Technique for Right Hemihepatectomies? The largest meta-analysis to date has shown that laparoscopic major hepatectomies have less blood loss, morbidity, and length of stay with similar operative times, transfusion rates, and completeness of resection compared with OLR.[38] The expert panel suggested that the feasibility, reproducibility, and implementation of left and right hepatectomies is sufficiently different that they should be considered separately. In experienced hands, laparoscopic right hemihepatectomies are associated with reduced hospital stay and blood loss. Mortality and completeness of resection are comparable with an open approach[39,40] (see R11.1, R11.2, R11.3, and R11.4).

What is the Role of the Laparoscopic Technique for Left Hemihepatectomies? Compared with an open approach, a laparoscopic approach is associated with reduced blood loss, morbidity, and hospital stay with comparable operative times, completeness of resection, and mortality[41,42] (see R12).

Topic 9: Minor Resections, Resections on Difficult Segments, Parenchymal Sparing/Anatomical Segmentectomies

What is the Role of the Laparoscopic Technique for Minor Liver Resections? A meta-analysis reports lower blood loss, transfusions rates, morbidity, and length of hospital stay for laparoscopic minor resections compared with open resections.[38] Laparoscopic left lateral sectionectomies are consistently associated with shorter hospital stay when compared with the open approach.[43] The evidence for a laparoscopic approach to segments 4b, 5, and en bloc cholecystectomy for gallbladder cancer is limited, but suggests similar perioperative outcomes to the open approach for T1 and T2 gallbladder cancers[44,45] (see R13.1 and R13.2).

What is the Role of the Laparoscopic Technique for Liver Resections in the "Difficult Segments (1, 4a, 7, and 8)"? The expert panel acknowledged that resections in these segments, especially when anatomical, are highly complex and require advanced expertise in LLS. Minor LLRs in segment 1, 4a, 7, and 8 are associated with greater operative time and blood loss than equivalent resections in the anterolateral segments. However, mortality and morbidity is not different.[46] Compared with OLR, LLR is associated with reduced blood loss and hospital stay.[47] A transthoracic approach and modifications to the patient's position may be useful alternatives to the classic approach to the postero-superior segments.[48,49] The perioperative outcomes of robotic and laparoscopic resections of the postero-superior segments appear to be similar in terms of blood loss, hospital stay, morbidity, and completeness of resection[50] (see R14.1, R14.2, and R14.3).

Is LLR Applicable for Parenchyma-sparing Procedures and Anatomic Segmentectomies? Laparoscopic and open sectionectomies have been found to have similar perioperative outcomes.[39] Various techniques, including a Glissonian approach, staining and indocyanine green fluorescence imaging have been suggested to facilitate a true anatomical segmentectomy.[51–53] Evidence for parenchyma-sparing LLR for centrally located lesions is limited. However, studies document R0 and recurrence rates that fall within the average published data[54,55] (see R15.1 and R15.2).

Section 4: Technique

Topic 10: Minimally Invasive Approaches, Surgical Devices, Intraoperative Staging, and Planning

What is the Role of the Hand-assisted Technique and Hybrid Procedures for Liver Resections? The evidence suggests that no 1 approach (open, hybrid, HALS, or pure laparoscopic) is totally superior in terms of operative or postoperative factors, but it has been suggested that HALS and hybrid techniques may serve as a bridge from open to laparoscopic surgery during the learning curve[56] (see R16).

What is the Role of the Robotic Approach for Liver Resections? The robotic approach has a longer operative time and higher costs compared with a laparoscopic approach, but comparable blood

loss, length of stay, resection margins, and morbidity.[57,58] Compared with an open approach, a study found total in-hospital cost to be reduced despite elevated operative cost[59] (see R17).

What is the Role of Intraoperative Ultrasound for LLR? The increased sensitivity of intraoperative ultrasound (compared with preoperative imaging and diagnostic laparoscopy) has been strongly suggested by numerous studies.[60,61] Multiple technical papers describe ultrasound as a necessary tool to investigate liver anatomy and tumor location, and to plan transection lines and margins[62,63] (see R18).

What are the Available Techniques for Parenchymal Transection? Multiple technical and comparative papers highlight the roles of differing transection devices. However, there is no universal agreement regarding the optimal technique[64–66] (see R19.1, R19.2, and R19.3).

Topic 11: Anatomic Major Resection (Formal Right/Left Hemi-hepatectomies)

What are the Available Safe Techniques for Inflow Control During Major Anatomical Resections? The majority of European centers have a preference for the hilar approach, regularly demonstrating its safety and reproducibility.[67] However, several centers outside of Europe report good outcomes with a Glissonian approach[51] (see R20).

What are the Available Safe Techniques During Right Hemihepatectomy? Although the anterior approach to liver transection, without prior liver mobilization, has been recommended by many a conventional approach with liver mobilization before transection is also possible and recommended by others. The choice between the 2 techniques depends on surgeon's preference, tumor size, and liver fragility. Whereas the hanging maneuver has been used and recommended by some surgeons its reproducibility has not yet been demonstrated[68,69] (see R21.1, R21.2, R21.3, R21.4, and R21.5).

Topic 12: Bleeding Control/Conversion

What are the Hemostatic Techniques During Laparoscopic Liver Resections? The use of an intermittent Pringle maneuver has been reported to have no detrimental effects on postoperative liver function.[70] Continuous hemi-hepatic inflow control has been shown to reduce blood loss compared with an intermittent Pringle maneuver with no detriment to postoperative liver function.[71] Several technical papers highlight the importance of a sufficient cuff of tissue when applying clips and endovascular staplers.[72] Lower intraoperative blood loss is reported in patients with a central venous pressure (CVP) lower than 5 cm H_2O.[73] The efficacy of stroke volume variation as an alternative to CVP monitoring has been demonstrated[74] (see R22.1, R22.2, R22.3, and R22.4).

When and How Should Conversions to Open Surgery Be Considered? Conversion during LLR is associated with higher postoperative morbidity; however, in comparison to planned OLR, the outcomes were found to be similar.[75] Risk factors for conversion include an increasing BMI, tumor size, and resection extent, and also resections in the postero-superior segments and cirrhosis.[36,76,77] In the case of conversion for significant vascular injury, temporary control of the bleeding source before conversion is highly recommended (see R23.1, R23.2, and R23.3).

Section 5: Implementation

Topic 13: Surgeon/Center/Learning Curves

What Training and Preparation Should Surgeons Pursue Before Performing Minor, Major, and Complex Liver Resections? With experience both operative time and blood loss decreases[78,79] and experience gained during minor resections may shorten the learning curve for major resections.[80] The learning curve for minor resections is suggested to be 60 cases[78] and that for major resections is 55 (having already developed experience on minor resections)[81] (see R24.1, R24.2, R24.3, and R24.4).

Which Centers Should Be Performing Laparoscopic Liver Resections? Laparoscopic liver surgery should not be developed in isolation from an open liver program. Major and complex LLS should be gradually implemented with increasing collective expertise for safe patient selection and management[82] (see R25.1, R25.2, and R25.3).

Should Laparoscopic Liver Resection Become Adopted in All Liver Surgical Centers? A meta-analysis has found that the laparoscopic approach offers fewer complications, decreased blood loss, and a shorter hospital stay with comparable oncological outcomes in selected patients.[38] Therefore, the guidelines confirm that all centers should implement a program of LLS and offer it to patients with the appropriate indications according to the local level of proficiency. Ideally, at least 2 surgeons proficient in LLS in each center are recommended (see R26).

Topic 14: Training/Registries

Who Should Be Undertaking Training and Mentoring Roles in LLR? With regards to trainers/mentors and registries/learned societies, no evidence-based studies are available. However, the learning curve for minor resections can significantly reduced by surgeons assisting one another.[83] The recommendation of the experts is that mentors and trainers must be experienced surgeons with a current and up-to-date knowledge of the literature, whereas registries are necessary for evaluation of LLR and individual surgeons/centers alike (this relates to R27, R28, and R29).

DISCUSSION

The European Guidelines Meeting for Laparoscopic Liver Surgery was devised to produce specific guideline statements to ensure the safe progression and dissemination of laparoscopic liver surgery. The guidelines produced further the work of the previous consensus meetings by providing specific guidance to both expert and training laparoscopic liver surgeons. The 67 guidelines combine the most up-to-date evidence with expert opinion to guide the dissemination of laparoscopic liver surgery. Each guideline reached at least a 95% consensus amongst the expert committee before its acceptance into the meeting. During the meeting, each statement was opened to a vote by all those in attendance (228 surgeons including the faculty). The median agreement was 88% (with at least 160 surgeons responding to each vote), demonstrating the support of these guidelines by those with a special interest in laparoscopic liver surgery. All statements were approved and endorsed by the independent validation committee.

The EGMLLS explored new areas in the application of laparoscopy in an ever-increasing cohort of patients, and provided guidance to the appropriateness of LLR for specific diseases. Indications have been refined taking into account-specific subcategories of high-risk patients and technically complex disease. Moreover, the guidelines re-define the classification of resections adding "technically major" resections, such as those in the postero-superior segments, to the established anatomical minor and major resections. Specific scenarios that require more experience were highlighted with the guidelines advocating caution dependent on the surgeon's expertise and available technical equipment.

The Southampton Guidelines state that when performed by expert surgeons, LLR offers significant advantages in terms of a reduced risk of postoperative ascites and liver decompensation in patients with cirrhosis. For patients with CRLM, LLR was deemed an appropriate option that offers significant benefits in terms of a shorter

hospital stay and lower complication rate. However, the need to adhere to a parenchymal sparing approach was stressed. The use of LLR for living donor hepatectomy is limited to a few highly specialized centers worldwide, but may now be regarded as standard practice for left lateral sectionectomy in adult-to-pediatric donation.

The Southampton Guidelines advocate that the laparoscopic approach should be considered standard practice for lesions in the left lateral and the anterior segments. The guidelines state that in expert hands, LLR for lesions in the postero-superior segments may maintain the advantages seen in the anterolateral segments. Subcategories of "high-risk" patients, such as the elderly and patients with high BMI, were no longer considered as contra-indications to LLR. Technically challenging resections such as repeat resections or 2-stage hepatectomies, resections for large lesions, and lesions in close proximity to the hilum are now considered possible by surgeons with extensive experiences in LLS.

The Southampton Guidelines highlight the difference in difficulty and outcomes between laparoscopic left and right hemi-hepatectomies. Hence, it was advised that their uptake occur at different points in the learning curve. Regarding inflow control and parenchymal transection, the guidelines state that the choice of technique is dependent on the characteristics of the disease and the surgeon's preference. Pringle maneuver and the management of intravascular volume to provide a low CVP are both essential to reduce blood loss during transection. And, as in open liver surgery, the need for intraoperative ultrasound was considered essential.

The guidelines regarding the implementation of LLS are of paramount importance in the EGMLLS. A background in open liver surgery and advanced laparoscopic skills before starting LLR are considered essential. The guidelines recommend fellowships, courses, and proctored programs to facilitate the training and development of laparoscopic liver surgeons. These fellowships should be conducted in established, high-volume centers that routinely perform minor, major, and complex major resections. Those providing supervision, as mentors and proctors, should themselves have already reached competency and are thus able to provide safe guidance during the training of less experienced surgeons. Importantly, it was recommended that each specialist center should offer a laparoscopic approach as part of its multidisciplinary management of liver disease and should ideally have a minimum of 2 surgeons competent in LLS to support, assist, and critique each other to aid development.

It is important to note that the majority of the evidence used in the production of these guidelines report data from specialist liver centers, which may represent a publication bias. However, this factor is of critical importance, as these guidelines should not be misconstrued as an invitation to begin performing laparoscopic liver surgery in the absence of experience and support. The authors must once again stress that laparoscopic liver surgery is complex and requires advanced laparoscopic skills, comprehensive experience of open liver surgery, and the support of an experienced team. Finally, the terms "experienced surgeons" and "selected patients" are not simple, rigid definitions, but represent a malleable spectrum where multiple confounding factors, which will evolve with time and vary between centers, must be considered. Although previous manuscripts have suggested that between 20 to 60 minor resections and 30 to 60 major resections (having already reached competency with minor resections) are required to overcome the learning curve,[78–81] the expert panel was in agreement that no specific number can be given to the number of resections performed for a surgeon to reach "competency," and patient factors must be weighed with respect to the experience of the surgeon and their team.

With the exponential growth of laparoscopic liver surgery, it will no doubt be necessary to review the current guidance with the passage of time to ensure that they continue to represent the most contemporary and highest level of evidence available to provide safe guidance in the dissemination of laparoscopic liver surgery.

CONCLUSIONS

The European Guidelines Meeting for Laparoscopic Liver Surgery has produced a set of clinical practice guidelines that have been independently validated for the safe development and progression of laparoscopic liver surgery. Using a robust methodology the Southampton Guidelines have amalgamated the available evidence and a wealth of experts' knowledge taking in consideration the relevant stakeholders' opinions and complying with the international methodology standards. These guidelines are not an endorsement for a novice to perform LLS without the appropriate training, and ideally LLS should be performed within the confines of an institution with an established support network and experience in liver surgery.

REFERENCES

1. Buell JF, Cherqui D, Geller DA, et al. The International Position on Laparoscopic Liver Surgery: The Louisville Statement, 2008. *Ann Surg*. 2009;250:825–830.
2. Wakabayashi G, Cherqui D, Geller DA, et al. Recommendations for laparoscopic liver resection: a report from the second International Consensus Conference held in Morioka. *Ann Surgery*. 2015;261:619–629.
3. Cherqui D. Evolution of laparoscopic liver resection. *Br J Surg*. 2016;103:1405–1407.
4. Abu Hilal M. Why do we need guidelines in laparoscopic liver surgery? *HPB (Oxford)*. 2017;19:287–288.
5. SIGN 50: A guideline developer's handbook. Scottish Intercollegiate Guidelines Network (SIGN). Available at: www.sign.ac.uk/guidelines/fulltext/50/index.html.
6. Dalkey NC, Helmer O. An experimental application of the Delphi method to the use of experts. *Manage Sci*. 1963;9:458–467.
7. AGREE II-GRS Instrument. Approval of Guidelines Research and Evaluation (AGREE). Available at: http://www.agreetrust.org/resource-centre/agree-ii-grs-instrument/.
8. Brouwers MC, Kho ME, Browman GP, et al. The Global Rating Scale complements the AGREE II in advancing the quality of practice guidelines. *J Clin Epidemiol*. 2012;65:526–534.
9. Luo LX, Yu ZY, Bai YN. Laparoscopic hepatectomy for liver metastases from colorectal cancer: a meta-analysis. *J Laparoendosc Adv Surg Techn*. 2014;24:213–222.
10. Clinicaltrial.gov. Trial Registry. U.S. National Institutes of Health. Available at: https://clinicaltrials.gov.
11. Cipriani F, Rawashdeh M, Stanton L, et al. Propensity score-based analysis of outcomes of laparoscopic versus open liver resection for colorectal metastases. *Br J Surg*. 2016;103:1504–1512.
12. Martínez-Cecilia F, Cipriani F, Vishal F, et al. Laparoscopic versus open liver resection for colorectal metastases in elderly and octogenarian patients. *Ann Surg*. 2017;265:1192–1200.
13. Montalti R, Tomassini F, Laurent S, et al. Impact of surgical margins on overall and recurrence-free survival in parenchymal-sparing laparoscopic liver resections of colorectal metastases. *Surg Endosc*. 2015;29:2736–2747.
14. Wei M, He Y, Wang J, et al. Impact of surgical margins on overall and recurrence-free survival in parenchymal-sparing laparoscopic liver resections of colorectal metastases. *PLoS One*. 2014;9:e87461.
15. Lupinacci RM, Andraus W, De Paiva Haddad LB, et al. Simultaneous laparoscopic resection of primary colorectal cancer and associated liver metastases: a systematic review. *Tech Coloproctol*. 2014;18:129–135.
16. Kim Y, Amini N, He J, et al. National trends in the use of surgery for benign hepatic tumours in the United States. *Surgery*. 2015;157:1055–1064.
17. Croome KP, Yamashita MH. Laparoscopic vs open hepatic resection for benign and malignant tumours: an updated meta-analysis. *Arch Surg*. 2010;145:1109–1118.
18. Kandil E, Noureldine SI, Koffron A, et al. Outcomes of laparoscopic and open resection for neuroendocrine liver metastatases. *Surgery*. 2012;152:1225–1231.
19. Xiong JJ, Altaf K, Javed MA, et al. Meta-analysis of laparoscopic vs open liver resection for hepatocellular carcinoma. *World J Gastroenterol*. 2012;18:6657–6668.
20. Takahara T, Wakabayashi G, Beppu T, et al. Long-term and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study. *J Hepatobiliary Pancreat Sci*. 2015;22:721–727.

21. Yoon YI, Kim KH, Kang SH, et al. Pure laparoscopic versus open right hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a propensity score matched analysis. *Ann Surg*. 2016;265:856–863.
22. Sposito C, Battiston C, Facciorusso A, et al. Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma. *Br J Surg*. 2016;103:871–880.
23. Shehta A, Han HS, Yoon YS, et al. Laparoscopic liver resection for hepatocellular carcinoma in cirrhotic patients: 10-year single-center experience. *Surg Endosc*. 2016;30:638–648.
24. Zhang Y, Huang J, Chen XM, et al. A comparison of laparoscopic versus open left hemihepatectomy for hepatocellular carcinoma. *Surg Laparosc Endosc Percutan Tech*. 2016;26:146–149.
25. Morise Z, Ciria R, Cherqui D, et al. Can we expand the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. *J Hepatobiliary Pancreat Sci*. 2015;22:342–352.
26. Harada N, Maeda T, Yoshizumi T, et al. Laparoscopic liver resection is a feasible treatment for patients with hepatocellular carcinoma and portal hypertension. *Anticancer Res*. 2016;36:3489–3497.
27. Cai X, Liang X, Tunan T, et al. Liver cirrhosis grading Child-Pugh B: a Goliath to challenge in laparoscopic liver resection? Prior experience and matched comparisons. *Hepatobiliary Surg Nutr*. 2015;4:391–397.
28. Samstein B, Griesemer A, Cherqui D, et al. Fully laparoscopic left-sided donor hepatectomy is safe and associated with shorter hospital stay and earlier return to work: A comparative study. *Liver Transpl*. 2015;21:768–773.
29. Cauchy F, Fuks D, Nomi T, et al. Benefits of laparoscopy in elderly patients requiring major liver resection. *J Am Coll Surg*. 2016;222:174–184.
30. Uchida H, Iwashita Y, Saga K, et al. Benefit of laparoscopic liver resection in high body mass index patients. *World J Surg*. 2016;22:3015–3022.
31. Cioffi L, Belli A, Fantini C, et al. Repeat liver surgery by laparoscopy for a malignant recurrence after previous open or laparoscopic resection. *Hepatoma Res*. 2015;1.
32. Shelat VG, Serin K, Samim M, et al. Outcomes of repeat laparoscopic liver resection compared to the primary resection. *World J Surg*. 2014;38:3175–3180.
33. Fuks D, Nomi T, Ogiso S, et al. Laparoscopic two-stage hepatectomy for bilobar colorectal liver metastases. *Br J Surg*. 2015;102:1684–1690.
34. Di Fabio F, Whistance R, Rahman S, et al. Exploring the role of laparoscopic surgery in two-stage hepatectomy for bilobar colorectal lover metastases. *J Laparoendosc Adv Tech A*. 2012;22:647–650.
35. Jun-hua Ai, Jian-wei Li, Chen J, et al. Feasibility and safety of laparoscopic liver resection for hepatocellular carcinoma with a tumor size of 5–10cm. *PLoS One*. 2013;8:723–728.
36. Shelat VG, Cipriani F, Basseres T, et al. Pure laparoscopic liver resection for large malignant tumors: does size matter? *Ann Surg Oncol*. 2014;22:1288–1293.
37. Yoon YS, Han HS, Cho JY, et al. Laparoscopic liver resection for centrally located tumors close to the hilum, major hepatic veins, or inferior vena cava. *Surg*. 2013;153:502–509.
38. Ciria R, Cherqui D, Geller A, et al. Comparative short-term benefits of laparoscopic liver resection: 9000 cases and climbing. *Ann Surg*. 2016;263:761–777.
39. Takahara T, Wakabayashi G, Konno H, et al. Comparison of laparoscopic major hepatectomy with propensity score matched open cases from the National Clinical Database in Japan. *J Hepatobiliary Pancreat Sci*. 2016;23:721–734.
40. Abu Hilal M, Di Fabio F, Teng MJ, et al. Single-centre comparative study of laparoscopic versus open right hepatectomy. *J Gastrointest Surg*. 2011;15:818–823.
41. Ye X, Ni K, Zhou X, et al. Laparoscopic versus open left hemihepatectomy for hepatolithiasis. *J Surg Res*. 2015;199:402–406.
42. Namgoong JM, Kim KH, Park GC, et al. Comparison of laparoscopic versus open left hemihepatectomy for left-sided hepatolithiasis. *Int J Med Sci*. 2014;11:127–133.
43. Ding G, Cai W, Qin M. Pure laparoscopic versus open liver resection in treatment of hepatolithiasis within the left lobes: a randomized trial study. *Surg Laparosc Endosc Percutan Tech*. 2015;25:392–394.
44. Agarwal AK, Javed A, Kalayarasan R, et al. Minimally invasive versus the conventional open surgical approach of a radical cholecystectomy for gallbladder cancer: a retrospective comparative study. *HPB (Oxford)*. 2015;17:536–541.
45. Itano O, Oshima G, Minagawa T, et al. Novel strategy for laparoscopic treatment of pT2 gallbladder carcinoma. *Surg Endosc*. 2015;29:3600–3607.
46. Lee W, Han HS, Yoon YS, et al. Comparison of laparoscopic liver resection for hepatocellular carcinoma located in the posterosuperior segments or anterolateral segments: a case-matched analysis. *Surgery*. 2016;160:1219–1226.
47. Scuderi V, Barkhatov L, Montalti R, et al. Outcome after laparoscopic and open resections of posterosuperior segments of the liver. *Br J Surg*. 2017;104:751–759.
48. Chiow AK, Lewin J, Manoharan B, et al. Intercostal and transthoracic trocars enable easier laparoscopic resection of dome liver lesions. *HPB (Oxford)*. 2015;17:299–303.
49. Ogiso S, Conrad C, Araki K, et al. Laparoscopic transabdominal with transdiaphragmatic access improves resection of difficult posterosuperior liver lesions. *Ann Surg*. 2015;262:358–365.
50. Montalti R, Scuderi V, Patriti A, et al. Robotic versus laparoscopic resections of posterosuperior segments of the liver: a propensity score-matched comparison. *Surg Endosc*. 2016;30:1004–1013.
51. Machado MA, Surjan RC, Basseres T, et al. The laparoscopic Glissonian approach is safe and efficient when compared with standard laparoscopic liver resection: results of an observational study over 7 years. *Surgery*. 2016;160:643–651.
52. Sakoda M, Ueno S, Iino S, et al. Anatomical laparoscopic hepatectomy for hepatocellular carcinoma using indocyanine green fluorescence imaging. *J Laparoendosc Adv Surg Tech A*. 2014;24:878–882.
53. Ishizawa T, Zuker NB, Kokudo N, et al. Positive and negative staining of hepatic segments by use of fluorescent imaging techniques during laparoscopic hepatectomy. *Arch Surg*. 2012;147:393–394.
54. Cipriani F, Shelat VG, Rawashdeh M, et al. Laparoscopic parenchymal-sparing resections for nonperipheral liver lesions, the diamond technique: technical aspects, clinical outcomes, and oncologic efficiency. *J Am Coll Surg*. 2015;221:265–272.
55. Conrad C, Ogiso S, Inoue Y, et al. Laparoscopic parenchymal-sparing liver resection of lesions in the central segments: feasible, safe, and effective. *Surg Endosc*. 2015;29:2410–2417.
56. Hasegawa Y, Koffron AJ, Buell JF, et al. Approaches to laparoscopic liver resection: a meta-analysis of the role of hand-assisted laparoscopic surgery and the hybrid technique. *J Hepatobiliary Pancreat Sci*. 2015;22:335–341.
57. Qiu J, Chen S, Chengyou D. A systematic review of robotic-assisted liver resection and meta-analysis of robotic versus laparoscopic hepatectomy for hepatic neoplasms. *Surg Endosc*. 2016;30:862–875.
58. Troisi RI, Patriti A, Montalti R, et al. Robot assistance in liver surgery: a real advantage over a fully laparoscopic approach? Results of a comparative bi-institutional analysis. *Int J Med Robot*. 2013;9:160–166.
59. Sham JG, Richards MK, Seo YD, et al. Efficacy and cost of robotic hepatectomy: is the robot cost-prohibitive? *J Robot Surg*. 2016;10:307–313.
60. Viganò L, Ferrero A, Amisano M, et al. Comparison of laparoscopic and open intraoperative ultrasonography for staging liver tumours. *Br J Surg*. 2013;100:535–542.
61. Milsom JW, Jerby BL, Kessler H, et al. Prospective, blinded comparison of laparoscopic ultrasonography vs. contrast-enhanced computerized tomography for liver assessment in patients undergoing colorectal carcinoma surgery. *Dis Colon Rectum*. 2000;43:44–49.
62. Aldrighetti L, Belli G, Boni L, et al. Italian experience in minimally invasive liver surgery: a national survey. *Updates Surg*. 2015;67:129–140.
63. Cherqui D, Figueroa R, Gelli M. Tips of totally laparoscopic left hepatectomy. *J Hepatobiliary Pancreat Sci*. 2016;23:E1–E4.
64. Berber E, Akyuz M, Aucejo F, et al. Initial experience with a new articulating energy device for laparoscopic liver resection. *Surg Endosc*. 2014;28:974–978.
65. Buell JF, Gayet B, Han HS, et al. Evaluation of stapler hepatectomy during a laparoscopic liver resection. *HPB (Oxford)*. 2013;15:845–850.
66. Dural C, Akyuz M, Yazici P, et al. Safety and efficacy of a new bipolar energy device for parenchymal dissection in laparoscopic liver resection. *Surg Laparosc Endosc Percutan Tech*. 2016;26:21–24.
67. Tzanis D, Shivathirthan N, Laurent A, et al. European experience of laparoscopic major hepatectomy. *J Hepatobiliary Pancreat Sci*. 2013;20:120–124.
68. Soubrane O, Schwarz L, Cauchy F, et al. A conceptual technique for laparoscopic right hepatectomy based on facts and oncologic principles: the caudal approach. *Ann Surg*. 2015;261:1226–1231.
69. Dokmak S, Ben Safta Y, Ftériche FS, et al. Pure laparoscopic right hepatectomy with the hanging maneuver for multiple hepatocellular adenomas. *Ann Surg Oncol*. 2014;21:3800–3801.
70. Dua MM, Worhunsky DJ, Hwa K, et al. Extra-corporeal Pringle for laparoscopic liver resection. *Surg Endosc*. 2015;29:1348–1355.
71. Zhang Y, Yang H, Deng X, et al. Intermittent Pringle's manoeuvre versus continuous hemihepatic vascular inflow occlusion using extra-glissonian approach in laparoscopic liver resection. *Surg Endosc*. 2016;30:961–970.

72. Abu Hilal M, Underwood T, Taylor MG, et al. Bleeding and haemostatis in laparoscopic liver surgery. *Surg Endosc*. 2009;24:572–277.
73. Jones RM, Moulton CE, Hardy KJ. Central venous pressure and its effect on blood loss during liver resection. *Br J Surg*. 1998;85:1058–1060.
74. Ratti F, Cipriani F, Reineke R, et al. Intraoperative monitoring of stroke volume variation versus central venous pressure in laparoscopic liver surgery: a randomized prospective comparative trial. *HPB*. 2016;18:136–144.
75. Cauchy F, Fuks D, Nomi T, et al. Risk factors and consequences of conversion in laparoscopic major liver resection. *Br J Surg*. 2015;102:785–795.
76. Ratti F, D'alessandro V, Cipriani F, et al. Influence of body habitus on feasibility and outcome of laparoscopic liver resections: a prosective study. *J Hepatobiliary Pancreat Sci*. 2016;23:373–381.
77. Troisi RI, Montalti R, Van Limmen JG, et al. Risk factors and management of conversions to an open approach in laparoscopic liver resection: analysis of 265 consecutive cases. *HPB*. 2014;16:75–82.
78. Vigano L, Laurent A, Tayar C, et al. The learning curve in laparoscopic liver resection: improved feasibility and reproducibility. *Ann Surg*. 2009;250:772–782.
79. Dagher I, Gayet B, Tzanis D, et al. International experience for laparoscopic major liver resection. *J Hepatobiliary Pancreat Sci*. 2014;21:732–736.
80. Hasegawa Y, Nitta H, Takahara T. Safely extending the indications of laparoscopic liver resection: when should we start laparoscopic major hepatectomy? *Surg Endosc*. 2017;31:309–316.
81. Van der Poel MJ, Besselink MG, Cipriani F, et al. Outcome and learning curve in 159 consecutive patients undergoing total laparoscopic hemihepatectomy. *JAMA Surg*. 2016;151:923–928.
82. Kluger MD, Vigano L, Barroso R, et al. The learning curve in laparoscopic major liver resection. *J Hepatobiliary Pancreat Sci*. 2013;20:131–136.
83. Goh BK, Chan CY, Wong JS, et al. Factors associated with and the outcomes of open conversion after laparoscopic minor hepatectomy: Initial experience at a single institution. *Surg Endosc*. 2015;29:2636–2642.

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ORIGINAL ARTICLE – HEPATOBILIARY TUMORS

A Systematic Review and Meta-Analysis Comparing the Short- and Long-Term Outcomes for Laparoscopic and Open Liver Resections for Hepatocellular Carcinoma: Updated Results from the European Guidelines Meeting on Laparoscopic Liver Surgery, Southampton, UK, 2017

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ABSTRACT

Background. The laparoscopic approach to liver resection has experienced exponential growth in recent years; however, its application is still under debate and objective, evidence-based guidelines for its safe future progression are needed.

Objective. The aim of this study was to perform a systematic review and meta-analysis comparing the short- and long-term outcomes of laparoscopic and open liver resections for hepatocellular carcinoma (HCC).

Methods. To identify all the comparative manuscripts reporting on laparoscopic and open liver resection for HCC, all published English-language studies with more than 10 cases were screened. In addition to the primary meta-analysis, four specific subgroup analyses were performed on patients with Child–Pugh A cirrhosis, resections for solitary tumors, and those undergoing minor and major resections. The quality of the studies was assessed using the Scottish Intercollegiate Guidelines Network (SIGN) methodology and the Newcastle–Ottawa Scale.

Results. From the initial 361 manuscripts, 28 were included in the meta-analysis. Five of these 28 manuscripts were specific to patients with Child–Pugh A cirrhosis (321 cases), 11 focused on solitary tumors (1003 cases), 16 focused on minor resections (1286 cases), and 3 focused on major resections (164 cases). Three manuscripts compared 1079 cases but could not be assigned to any of the above subanalyses. In general terms, short-term outcomes were favorable when using a laparoscopic approach, especially in minor resections. The only advantage seen with an open approach was reduced operative time during major liver

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Ruben Ciria and Irene Gomez-Luque contributed equally to the development of this manuscript.

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resections. No differences in long-term outcomes were observed between the approaches.

Conclusions. Laparoscopic liver resection for HCC is feasible and offers improved short-term outcomes, with comparable long-term outcomes as the open approach.

Liver resection is a first-line option in very early- and early-stage disease, and a secondary option in intermediate-stage hepatocellular carcinoma (HCC).[1–4] In 1995 and 1996, the first minimally invasive liver resection series for HCC was reported.[5,6] Since then, a minimally invasive approach to liver resections has been used in the treatment of a myriad of conditions, and exponential dissemination has been experienced.[7] However, at the last Consensus Conference held in Morioka in 2014,[8] the laparoscopic approach for HCC was still considered in need of standardization to allow for its safe development.

A laparoscopic approach to liver resections offers improved short-term outcomes compared with the traditional open approach.[7] Recent meta-analyses specific to HCC have reported that a laparoscopic approach is associated with improved outcomes, however these studies have considered all resections and lesions as a single homogenous group, which may result in potential bias and hence inaccuracies in the conclusions.[9–12] In addition, these studies have only considered either short- or long-term outcomes, leaving a need for a detailed, holistic assessment of the role of laparoscopic liver resection (LLR) in the management of HCC. A recent multicenter study by Cipriani et al.[13] demonstrated that a laparoscopic approach provided the same short-term outcomes in patients with both Child–Pugh A and Child–Pugh B cirrhosis, and suggested that the current guidelines regarding resections in cirrhosis could be expanded using a laparoscopic approach.

In the context of the European Guidelines Meeting on Laparoscopic Liver Surgery (EGMLLS) held in Southampton, UK, from 9 to 11 February 2017, an updated meta-analysis was prepared in which five sub-meta-analyses were performed after assessing the patterns of all available studies comparing the laparoscopic and open approaches in the management of HCC.

PATIENTS AND METHODS

Aims of the Study

Our primary aim was to amalgamate, weigh, and summarize the current evidence regarding the short- and long-term outcomes of laparoscopic and open liver resections for the management of HCC, by systematic review and meta-analysis, while our secondary aims were to assess the distribution of available studies with regard to disease stage and resection type, and perform secondary subgroup meta-analyses by grouping like studies in order to increase the level of evidence for specific disease stages and resection types.

Search Strategy and General Considerations

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[14] The Pubmed, Embase, Cochrane Library, and Web of Science electronic databases were searched using the following search strategy: ((hepatocellular[Title] OR HCC) AND (laparoscopic[Title] OR laparoscopy[Title] OR minimally[Title] OR hybrid[Title])) and their associated combinations of controlled vocabulary (Medical Subject Heading [MeSH]) terms. The final search was performed on 20 June 2017.

Study Selection

Inclusion criteria were human comparative studies written in English that included only laparoscopic versus open procedures from the last 15 years and selected the last largest series in case of detection of duplicates. Reviews, editorials, case reports, or letters were excluded, as were manuscripts in which radiofrequency, chemoembolization, liver transplant, and robotic or hybrid procedures were performed. Review articles were examined for potential additional references, and duplicates were identified by matching both author names and publication centers. After initial screening, full-text versions of the selected manuscripts were obtained. Two reviewers (RC and IG-L), as well as an independent third reviewer (MH or FC) in cases where consensus could not be reached, individually assessed each manuscript and rejected those that failed to meet the inclusion criteria.

Definitions

Considering the aims of our study, the following definitions and patterns were considered:

1. Resection type was based on the proposal from the Louisville Consensus meeting in 2008 [15], with minor resections involving two or fewer Couinaud segments and major resections involving three or more continuous Couinaud segments.
2. Each manuscript was assessed to establish if results reported could be applicable to more than one of the subgroups. If so, the results were separated and individually analyzed within their subgroups.

3. Combined series were defined as those reporting a mixture of minor/major resections that could not be separated and analyzed separately, and hence could not be included within the above subgroups.

Variables and Endpoints (endpoints shown in bold).

1. Short-term outcomes (intraoperative parameters): operative time (minutes), operative blood loss (mL), and number of patients requiring blood transfusion (%).
2. Short-term outcomes (postoperative parameters): total number of early (< 30 days) complications (%), duration of postoperative hospital stay (days), mean resection margin (mm), post-hepatectomy liver failure (PHLF) [and subcategories as defined by the International Study Group of Liver Surgery (ISGLS) in 2011[16] and perioperative (30-day, 90-day, or undefined) mortality.
3. Long-term outcomes. 1-, 3-, and 5-year overall survival (OS); 1, 3-, and 5-year disease-free recurrence.

Quality Assessment of the Studies Included in the Meta-Analysis

First Quality Assessment The first quality assessment was performed in accordance with the Scottish Intercollegiate Guidelines Network (SIGN).[17]

Second Quality Assessment The second quality assessment was performed in accordance with the Newcastle–Ottawa Quality Assessment Scale (NOS) for cohort and case–control studies (Ottawa Hospital Research Institute; available at http://www.ohri.ca/programs/clinical_epidemiology/oxford.htm). The criteria for 'representativeness of cases' were considered as consecutive, or representative series of cases without potential selection bias. Specifically, no star was given if cases included were not matched by year of inclusion (due to potential selection bias) and/or different surgeons and/or an inclusion period > 10 years (due to potential technical bias). Similarly, equal distribution of type and severity of underlying liver disease was an exclusion criteria that was given a star. For the 'control for important factor' rating, two stars were given if laparoscopic and open cases were matched by age, sex, American Society of Anesthesiologists (ASA) score, body mass index, type of resection, Child–Pugh score, and number and size of the lesions. If any of these factors were not specifically mentioned or were not correctly matched, only one star was given. If two or more of these factors were not correctly matched or were not mentioned, no stars were given.

Statistical Analysis

Analyses were performed using log odds ratios (OR) with 95% confidence intervals (CIs) for dichotomous variables, and weighted mean differences (WMD) with 95% CIs for continuous variables. For dichotomous variables in which any observed value was 0, it may not be possible to calculate the OR, and thus rate differences were used. The standard heterogeneity test used was the *I*-square statistic. Based on the method reported by DerSimonian and Laird,[18] substantial significance was set when the p value was < 0.10 and a random-effects model was used.[19] An *I*-square value of < 25% was defined to represent low heterogeneity, between 25 and 50% was defined as moderate heterogeneity, and > 50% was defined as high heterogeneity. Publication bias was also assessed visually using a funnel plot for standard error by effect size. Each calculation for every group had a specific funnel plot. Data that were not significantly heterogeneous ($p > 0.1$) were calculated using a fixed-effects model using the Mantel–Haenszel method.[20] OpenMEE software, based on Open MetaAnalyst Software, was used for statistical analyses.[21,22]] To perform meta-analyses, means and standard deviations (SDs) were needed, and estimations of means and SDs were performed to avoid discarding important studies. According to a recent publication from Wan et al.[23], in the event that a manuscript reported data in different measures other than mean and SD, two different scenarios were considered, as reported in our previous meta-analysis.[7] For the meta-analysis, the authors decided to perform calculations only if at least three series could be identified for each variable, avoiding results derived from analyses of two reports.

RESULTS

Eligible Studies and Final Count

From the initial 361 manuscripts identified in the searches, 34 comparative studies remained after the inclusion and exclusion criteria were applied (electronic supplementary material [ESM] 1). Six manuscripts[24–29] did not reach a minimum requirement of acceptable quality (by SIGN scoring) or 6 points (by NOS) and were subsequently discarded (Table 1), resulting in 28 manuscripts being considered for the systematic review and meta-analysis. Five of these 28 manuscripts were specific to patients with Child–Pugh A cirrhosis (321 cases),[30–34] 16 focused on minor resections (1286 cases),[3,32–46] three focused on major resections (164 cases),[30,47,48] and 11 focused on solitary tumors (1003 cases).[31,34,36,45,49–54] The remaining three manuscripts (comparing 1079 cases) could not be individually classified as they were propensity score or 2:1

TABLE 1 Overall quality analysis from all comparative studies including NOS and SIGN scores

Characteristics of the studies included in the meta-analysis for HCC patients															
Author (city/province, country)	Year	*N* lap	*N* open	Etiology	Conversion	Quality assessment by NOS									SIGN
						Selection				Comparability	Exposure			Quality judgment (maximum nine stars)	
						Adequate definition of cases	Representativeness of cases	Selection of controls	Definition of controls	Control for important factors	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-response rate		
Child–Pugh A															
Zhang et al.[30] (China)	2016	20	25	HCC	–	–	*	–	*	*	*	*	*	******	+ Acceptable
Ahn et al.[31] (Daegu, Korea)	2014	52 (51)	150 (51)	HCC	Excluded	*	*	–	*	**	*	*	*	********	++ High
Kim et al.[49] (Seoul, Korea)	2014	29	29	HCC	23.3%	–	*	–	*	*	*	*	*	******	+ Acceptable
Truant et al.[33] (Lille, France)	2011	36	53	HCC	7 (19.4%)	–	–	–	*	**	*	*	*	******	+ Acceptable
Lee et al.[24] (Hong Kong, China)	2011	33	50	HCC	6 (18.2%)	–	–	–	*	*	*	*	*	*****	+ Acceptable
Laurent et al.[34] (Créteil, France)	2003	13	14	HCC	2 (15%)	–	*	–	*	*	*	*	*	******	+ Acceptable
Minor - only															
Sposito et al.[3] (Italy)	2016	43 (43)	226 (43)	HCC	Excluded	*	*	–	*	**	*	*	*	********	++ High
Zhang et al.[35] (China)	2016	31	33	HCC	0 (0%)	–	*	–	*	*	*	*	*	******	+ Acceptable
Luo et al.[36] (Chengdu, China)	2015	53	53	HCC	Excluded	–	*	–	*	*	*	*	*	******	+ Acceptable
Beppu et al.[37] (Kumamoto, Japan)	2015	89 (52)	180 (52)	HCC	2 (2.2%)	*	*	–	*	*	*	*	*	*******	++ High
Xiao et al.[25] (China)	2015	41	86	HCC	3 (7.32%)	–	*	–	*	*	*	*	*	*****	++ High
Cheung et al.[38] (Hong Kong, China)	2015	24	29	HCC	–	–	*	–	*	*	*	*	*	******	+ Acceptable
Yamashita et al.[39] (Fukuoka, Japan)	2014	63	99	HCC	–	–	*	–	*	*	*	*	*	******	+ Acceptable
Memeo et al.[40] (Créteil, France)	2014	45	45	HCC	0	–	*	–	*	*	*	*	*	******	+ Acceptable
Kim et al.[32] (Seoul, Korea)	2014	29	29	HCC	23.3%	–	*	–	*	*	*	*	*	******	+ Acceptable
Kanazawa et al.[41] (Osaka, Japan)	2013	28	28	HCC	5/23 hybrid (21.73%)	–	–	–	*	**	*	*	*	******	+ Acceptable
Cheung et al.[42] (Hong Kong, China)	2013	32	64	HCC	6 hand-assist (18.8%)	–	–	–	*	**	*	*	*	******	+ Acceptable
Kobayashi et al.[43] (Osaka, Japan)	2013	24	27	HCC	–	–	*	–	*	*	*	*	*	******	+ Acceptable
Hu et al.[26] (Jiangsu, China)	2011	30	30	HCC	–	–	*	–	*	*	*	*	*	******	– Low
Truant et al.[33] (Lille, France)	2011	36	53	HCC	7 (19.4%)	–	–	–	*	**	*	*	*	******	+ Acceptable

Outcomes after laparoscopic approach of HCC

TABLE 1 continued

Lee et al.[24] (Hong Kong, China)	2011	33	50	HCC	6 (18.2%)	–	–	–	❄	❄	❄	❄	❄	❄❄❄❄❄	+ Acceptable
Ker et al.[27] (Kaohsiung, China)	2011	116	208	HCC	6 (5.2%)	–	–	–	❄	–	❄	❄	❄	❄❄❄❄	+ Acceptable
Aldrighetti et al.[28] (Milan, Italy)	2010	16	16	HCC	1 (6.25%)	–	–	–	❄	–	❄	❄	❄	❄❄❄❄	+ Acceptable
Endo et al.[29] (Oita, Japan)	2009	10	11	HCC	Lap-assisted	–	–	–	❄	–	❄	❄	❄	❄❄❄❄	+ Acceptable
Belli et al.[44] (Naples, Italy)	2007	23	23	HCC	1 (4.3%)	–	–	–	❄	❄❄	❄	❄	❄	❄❄❄❄❄❄	++ High
Kaneko et al.[45] (Tokyo, Japan)	2005	30	28	HCC	3.3%	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	+ Acceptable
Laurent et al.[34] (Créteil, France)	2003	13	14	HCC	2 (15%)	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	+ Acceptable
Shimada et al.[46] (Fukuoka, Japan)	2001	17	38	HCC	0	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	+ Acceptable
Major - only															
Zhang et al.[30] (China)	2016	20	25	HCC	–	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	+ Acceptable
Komatsu et al.[47] (France)	2016	38	38	HCC	–	–	❄	–	❄	❄❄	❄	❄	❄	❄❄❄❄❄❄❄	+ Acceptable
Cho et al.[48] (Seoul, Korea)	2015	24	19	HCC	3 (12.5%)	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	+ Acceptable
Solitary tumors															
Luo et al.[36] (Chengdu, China)	2015	53	53	HCC	Excluded	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	+ Acceptable
Xiao et al.[25] (China)	2015	41	86	HCC	3 (7.32%)	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄	++ High
Ahn et al.[31] (Daegu, Korea)	2014	52 (51)	150 (51)	HCC	Excluded	❄	❄	–	❄	❄❄	❄	❄	❄	❄❄❄❄❄❄❄❄	++ High
Kim et al.[49] (Seoul, Korea)	2014	70	76	HCC	6 (8.57%)	❄	❄	–	❄	❄❄	❄	❄	❄	❄❄❄❄❄❄❄❄	++ High
Ai et al.[50] (Putian, China)	2013	97	178	HCC	9.3%	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	+ Acceptable
Hu et al.[26] (Jiangsu, China)	2011	30	30	HCC	–	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	– Low
Kim et al.[51] (Gwangju, Korea)	2011	26	29	HCC	3 (10.3%)	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	+ Acceptable
Nguyen et al.[52] (Pittsburgh, USA)	2011	17	20	HCC	–	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	+ Acceptable
Ker et al.[27] (Kaohsiung, China)	2011	116	208	HCC	6 (5.2%)	–	–	–	❄	–	❄	❄	❄	❄❄❄❄	+ Acceptable
Tranchart et al.[53] (Paris, France)	2010	42	42	HCC	2 (4.7%)	–	❄	–	❄	❄	❄	❄	❄	❄❄❄❄❄❄	+ Acceptable
Aldrighetti et al.[28] (Milan, Italy)	2010	16	16	HCC	1 (6.25%)	–	–	–	❄	–	❄	❄	❄	❄❄❄❄	+ Acceptable
Endo et al.[29] (Oita, Japan)	2009	10	11	HCC	Lap-assisted	–	–	–	❄	–	❄	❄	❄	❄❄❄❄	+ Acceptable

TABLE 1 continued

Lai et al.[54] (Chai Wan, Hong Kong)	2009	25	33	HCC	1 (4%)	–	*	–	*	*	*	*	*	******	+ Acceptable
Kaneko et al.[45] (Tokyo, Japan)	2005	30	28	HCC	3.3%	–	*	–	*	*	*	*	*	******	+ Acceptable
Laurent et al.[34] (Créteil, France)	2003	13	14	HCC	2 (15%)	–	*	–	*	*	*	*	*	******	+ Acceptable
Shimada et al.[46] (Fukuoka, Japan)	2001	17	38	HCC	0	–	*	–	*	*	*	*	*	******	+ Acceptable
Combined															
Takahara et al.[55] (Japan)	2015	436 (387)	2969 (387)	HCC	25 (6.5%)	*	*	–	*	**	*	*	*	********	++ High
Han et al.[56] (Seoul, Korea)	2015	232 (88)	157 (88)	HCC	8 (9.1%)	*	*	–	*	*	*	*	*	********	++ High
Lee et al.[57] (Toronto, Canada)	2015	43	86	HCC	6 (14%)	–	*	–	*	*	*	*	*	******	++ High

Studies marked in bold were discarded because they had NOS < 7 stars or low scoring in the SIGN analysis

SIGN Scottish Intercollegiate Guidelines Network, *NOS* Newcastle–Ottawa Scale, *HCC* hepatocellular carcinoma, *lap* laparoscopic surgery, *open* open surgery

matched, and hence independent results could not be obtained;[55–57] these were analyzed as 'combined' resections. All baseline results are depicted in ESM 2 and 3.

Solitary Tumors

A total of 11 studies were identified, including 562 open resections and 441 LLRs for solitary HCC. Operative times were equal between the groups, but all other short-term outcomes, including complication rates (heterogeneity p value = 0.095; I-squared = 38%; OR 2.42 [95% CI 1.695–3.456]; $p < 0.001$), blood loss (heterogeneity p value ≤ 0.001; I-squared = 78%; standardised mean difference [SMD] −0.476 [95% CI −0.828 to −0.124]; $p < 0.008$), transfusions (heterogeneity p value = 0.75; I-squared = 0%; OR 1.703 [95% CI 1.067–2.717]; $p < 0.026$), hospital stay (heterogeneity p value ≤ 0.001; I-squared = 78%; SMD −0.786 [95% CI −1.089 to −0.483]; $p < 0.001$), and resection margins (heterogeneity p-value = 0.88; I-squared = 0%; SMD 0.218 [95% CI 0.064–0.371]; $p = 0.005$), favored a laparoscopic approach (Figs. 1, 2). Mortality and PHLF were not significantly different between the groups (ESM 4), and there were no significant differences in 1-, 3-, and 5-year OS and DFS (Figs. 3, 4).

Child–Pugh A Resections

Five studies including 172 open procedures and 149 laparoscopic procedures were analyzed. Both complication rates (heterogeneity p value < 0.001; I-squared = 81%; OR 0.256 [95% CI 0.066–0.446]; $p = 0.008$) and hospital stay (heterogeneity p value ≤ 0.001; I-squared = 87%; SMD −1.037 [95% CI −1.718 to −0.357]; $p = 0.003$) favored a laparoscopic approach (Figs. 1, 2). Perioperative mortality was equivalent in both the open and laparoscopic approaches (ESM 4). Long-term outcomes were insufficiently reported, and hence only three manuscripts were analyzed. These demonstrated no difference in OS and disease-free survival (DFS) between the two groups (Figs. 3, 4).

Minor-Only Liver Resections

Sixteen manuscripts were identified that included 628 open procedures and 658 laparoscopic procedures. The short-term outcomes for complication rates (heterogeneity p value < 0.001; I-squared = 75%; OR 0.175 [95% CI 0.093–0.257]; $p < 0.001$), blood loss (heterogeneity p value ≤ 0.001; I-squared = 85%; SMD −0.685 [95% CI −1.012 to −0.357]; $p < 0.001$), transfusion rate (heterogeneity p value = 0.13; I-squared = 20%; OR 0.027 [95% CI 0.001–0.053]; $p < 0.001$), and hospital stay (heterogeneity p value ≤ 0.001; I-squared = 75%; SMD −0.837 [95% CI −1.083 to −0.590]; $p < 0.001$) all favored a laparoscopic approach (Figs. 1, 2), with no difference in operative time and resection margin (Fig. 3). As with solitary resections, mortality and PHLF were not different between the groups (ESM 4). Long-term outcomes

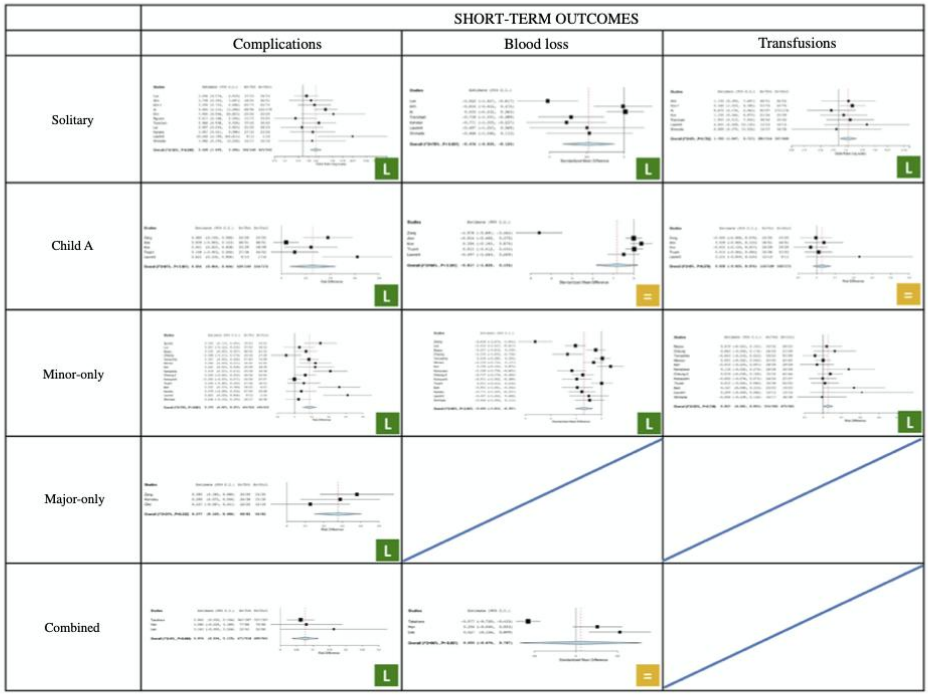

FIG. 1 Meta-analysis of short-term outcomes (I)

(Figs. 3, 4) were similar between both approaches, except for the 1-year DFS (heterogeneity p value = 0.019; I-squared = 66%; OR 0.133 [95% CI 0.001–0.265]; $p < 0.048$), which was in favor of the laparoscopic approach.

Major-Only Liver Resections

Only limited data were available for major liver resections and no long-term data could be retrieved. Regarding short-term outcomes, the complication rate was lower when using a laparoscopic approach (heterogeneity p value = 0.232; I-squared = 31%; OR 0.277 [95% CI 0.149–0.406]; $p < 0.001$) [Fig. 1]. However, operative time was shorter for OLR (heterogeneity p value = 0.015; I-squared = 76%; SMD 0.835 [95% CI 0.155–1.516]; $p = 0.016$) [Fig. 2]. There was a trend towards a shorter hospital stay in the laparoscopic group, but this did not reach statistical significance.

Combined Studies

The three manuscripts that contained combined studies did not have any long-term data available. Regarding short-term outcomes, the rate of complications (heterogeneity p value = 0.469; I-squared = 0%; OR 0.076 [95% CI 0.036–0.115]; $p < 0.001$) [Fig. 1] and hospital stay (heterogeneity p value ≤ 0.001; I-squared = 92%; SMD −0.788 [95% CI −1.339 to −0.237]; $p = 0.005$) favored a laparoscopic approach, but the remaining short-term outcomes (operative time and blood loss) were not different.

Publication Bias Analysis

All the series allocated to each subanalysis were independently assessed for bias in each variable (ESM 5, 6, 7, and 8).

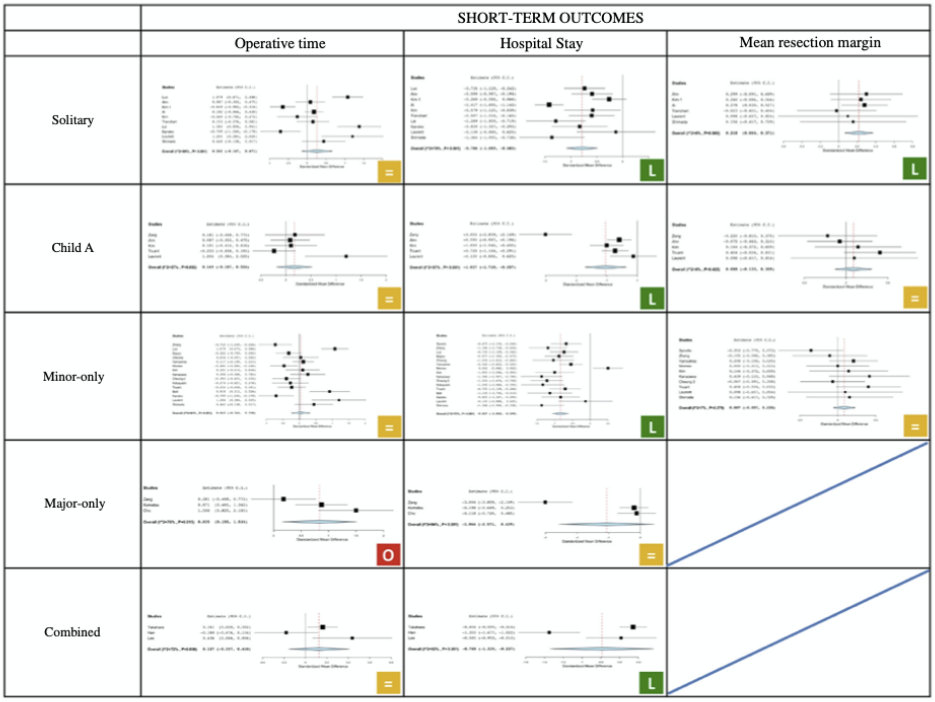

FIG. 2 Meta-analysis of short-term outcomes (II)

DISCUSSION

The largest meta-analysis to date suggests that a significant proportion of LLRs are performed for the management of HCC, as 3072 of 6190 LLRs for malignancies were performed for HCC [7]. In 2017, Southampton hosted the EGMLLS, with the specific aim of presenting and validating the first set of evidence-based guidelines for laparoscopic liver surgeons [58]. In this setting, the aim of our study was to perform a high-quality meta-analysis examining the short- and long-term outcomes after LLR for HCC. The results of our meta-analysis demonstrate that for most short-term outcomes, a laparoscopic approach provides better results than an open approach.

During and after liver resection, blood loss and transfusions are important factors that impact not only early postoperative outcomes but also long-term results with an increased risk of cancer recurrence and decreased patient survival [59,60]. When it came to these variables (blood loss and transfusions), our meta-analysis showed that the laparoscopic approach did better than the open route, especially within the subgroup analyses for solitary tumors and minor resections. Similarly, the complication rate was favorable for a laparoscopic approach in all analyses. These results suggest that a laparoscopic approach is similar, if not better than, the open approach for the management of HCC in patients with Child–Pugh A cirrhosis, solitary tumors, and those undergoing minor resections in terms of short-term outcomes.

It should be remarked that limited information was available for specific postoperative variables such as mortality (not clearly defined as perioperative, or 30- or 90-days) and PHLF. Because of this, perioperative mortality was all put together in our analysis. Similarly, PHLF could not be individually screened by the ISGLS groups and was thus analyzed as a single category. It should be encouraged that all research teams perform statistics for their manuscripts using currently validated classifications rather than institutional or self-raised criteria. In addition, limited information was available for long-term outcomes

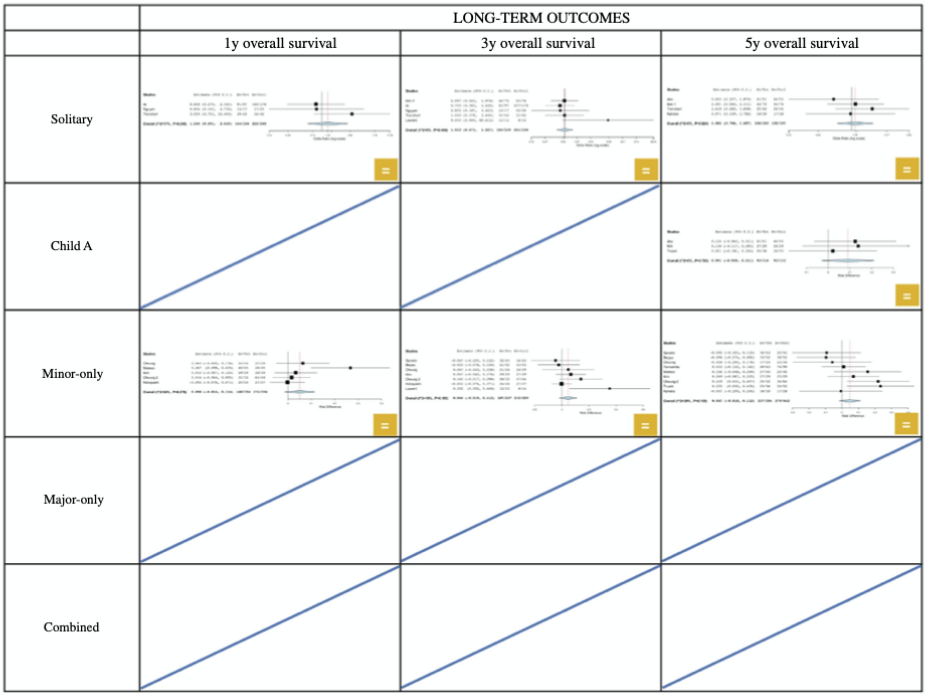

FIG. 3 Meta-analysis of long-term outcomes (I)

of the surgical management of HCC. Only data for 3- and 5-year survival provided sufficient detail for analysis. For this, a trend towards improved survival was associated with a laparoscopic approach, however this did not reach statistical significance. DFS followed a similar pattern, with the noteworthy exception of an improved rate at 1 year for laparoscopic minor resections. Although statistically significant, this difference should be considered with caution and no strong conclusions should be drawn from this finding as only five studies with a slight dispersion were included in the analysis.

Previous meta-analyses have already reported the results of open resection versus LLR for HCC;[10–13,61] however, most of them focused only on short-term outcomes. Only the studies by Zhou et al.[10] and Fancellu et al.[11] analyzed long-term OS and DFS (both in 2011), including few reports in which different types of resection were mixed. To give stronger evidence to the results currently available, we put together short- and long-term outcomes in each category that we could identify. It should be noted that the I2 score was high in many of the comparisons and thus decreased confidence in the estimates may be considered a limitation to our manuscript. In order to minimize this heterogeneity, our meta-analysis included several steps that tried to minimize biases. As per the EGMLLS methodology, we initially performed an extensive literature review with strong quality discrimination. For this purpose, we used two well-validated quality assessment tools to obtain the best quality of evidence—the SIGN methodology and the NOS. Manuscripts that were rated as low quality in the SIGN and/or received less than six stars in the NOS were discarded. Second, we performed subgroup meta-analyses specifically examining patients with Child–Pugh A cirrhosis, solitary tumors, and those undergoing minor and major liver resections. Additional literature searches were performed for 'portal hypertension' (using platelet count and/or esophageal varices), multicentric HCC, Barcelona Liver Clinic (BCLC)-A or -B, or severe cirrhosis, but no comparative series were available. Finally, all meta-analyses performed to date used the methodology of Hozo

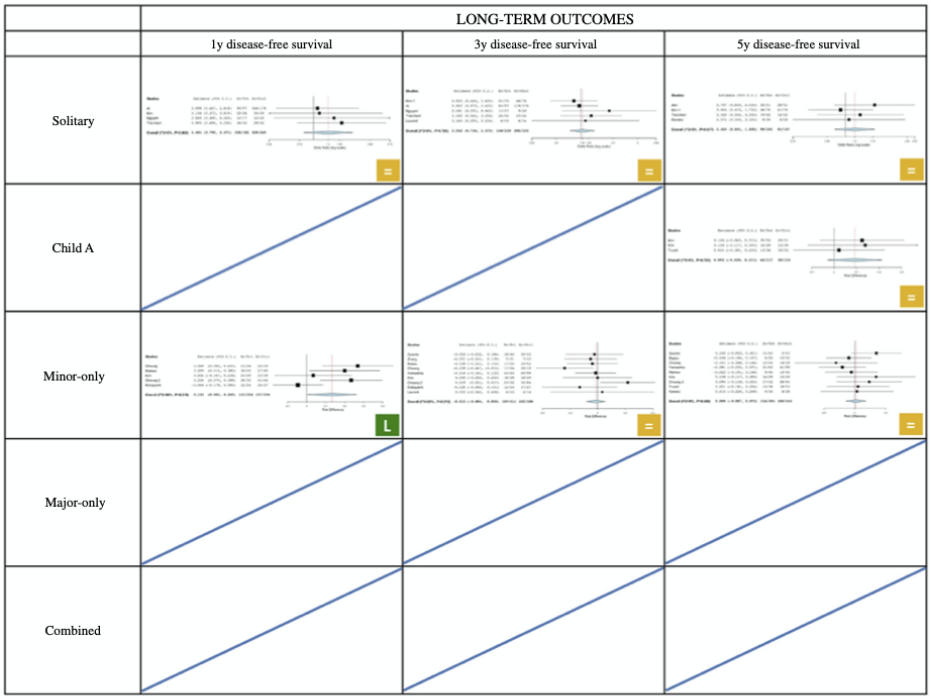

FIG. 4 Meta-analysis of long-term outcomes (II)

et al.[62], however we have chosen to use the methodology of Wan et al.[23], which has recently been demonstrated to achieve more precise calculations of mean and SD, and which in turn allows for more accurate conclusions.

CONCLUSIONS

Liver surgery for HCC in cirrhotic patients is considered more dangerous due to the potential for increased morbidity, especially liver decompensation, and higher postoperative mortality. Due to refinements in surgical technique, anesthetic management, and perioperative care, liver resections are now considered a standard practice for early-stage tumors in cirrhotic patients with well-compensated liver function. The results of the present meta-analysis demonstrate that a minimally invasive approach may be superior to an open approach with respect to short-term outcomes for patients with Child–Pugh A cirrhosis, solitary tumors, and minor resections. In the long-term setting, the results demonstrate that a minimally invasive approach is comparable to an open approach in terms of overall and DFSs. Considering the current evidence, it may be concluded that LLRs for HCC are safe and may be considered a standard practice in specific settings.

REFERENCES

1. El-Serag HB. Hepatocellular carcinoma. *N Engl J Med.* 2011;365(12):1118–27.
2. Clavien P-A, Lesurtel M, Bossuyt PM, Gores GJ, Langer B, Perrier A. Recommendations for liver transplantation for hepatocellular carcinoma: an international consensus conference report. *Lancet Oncol.* 2012;13(1):e11–e22.
3. Sposito C, Battiston C, Facciorusso A, Mazzola M, Muscarà C, Scotti M et al. Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma. *Br J Surg.* 2016;103(7):871–80.
4. Ciria R, López-Cillero P, Gallardo AB, Cabrera J, Pleguezuelo M, Ayllón MD et al. Optimizing the management of patients with BCLC stage-B hepatocellular carcinoma: modern surgical resection as a feasible alternative to transarterial chemoemolization. *Eur J Surg Oncol.* 2015;41(9):1153–61.

5. Hashizume M, Takenaka K, Yanaga K, Ohta M, Kajiyama K, Shirabe K et al. Laparoscopic hepatic resection for hepatocellular carcinoma. *Surg Endosc.* 1995;9(12):1289–91.
6. Kaneko H, Takagi S, Shiba T. Laparoscopic partial hepatectomy and left lateral segmentectomy: technique and results of a clinical series. *Surgery.* 1996;120(3):468–75.
7. Ciria R, Cherqui D, Geller DA, Briceño J, Wakabayashi G. Comparative short-term benefits of laparoscopic liver resection: 9000 cases and climbing. *Ann Surg.* 2016;263(4):761–77.
8. Wakabayashi G, Cherqui D, Geller DA, Buell JF, Kaneko H, Han H-S et al. Recommendations for laparoscopic liver resection: a report from the second international consensus conference held in Morioka. *Ann Surg.* 2015;261(4):619–29.
9. Chang L, Wang Y, Zhang J, Guo T. The best strategy for HCC patients at each BCLC stage: a network meta-analysis of observational studies. *Oncotarget.* 2017;8(12):20418–27.
10. Zhou Y-M, Shao W-Y, Zhao Y-F, Xu D-H, Li B. Meta-analysis of laparoscopic versus open resection for hepatocellular carcinoma. *Dig Dis Sci.* 2011;56(7):1937–43.
11. Fancellu A, Rosman AS, Sanna V, Nigri GR, Zorcolo L, Pisano M et al. Meta-analysis of trials comparing minimally-invasive and open liver resections for hepatocellular carcinoma. *J Surg Res.* 2011;171(1):e33–45.
12. Morise Z, Ciria R, Cherqui D, Chen K-H, Belli G, Wakabayashi G. Can we expand the indications for laparoscopic liver resection? A systematic review and meta-analysis of laparoscopic liver resection for patients with hepatocellular carcinoma and chronic liver disease. *J Hepatobiliary Pancreat Sci.* 2015;22(5):342–52.
13. Cipriani F, Fantini C, Ratti F, Lauro R, Tranchart H, Halls M et al. (2017) Laparoscopic liver resections for hepatocellular carcinoma. Can we extend the surgical indication in cirrhotic patients? *Surg Endosc*. 30(suppl 3):61–70.
14. Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ.* 2009;339:b2535.
15. Buell JF, Cherqui D, Geller DA, O'Rourke N, Iannitti D, Dagher I et al. The international position on laparoscopic liver surgery: the Louisville statement, 2008. *Ann Surg.* 2009;250(5):825–30.
16. Rahbari NN, Garden OJ, Padbury R, Brooke-Smith M, Crawford M, Adam R et al. Posthepatectomy liver failure: a definition and grading by the International Study Group of Liver Surgery (ISGLS). *Surgery.* 2011;149(5):713–24.
17. Petrie JC, Grimshaw JM, Bryson A. The Scottish intercollegiate guidelines network initiative: getting validated guidelines into local practice. *Health Bull (Edinb).* 1995;53(6):345–8.
18. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Controll Clin Trials.* 1986;7(3):177–88.
19. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003;327(7414):557–60.
20. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst.* 1959;22(4):719–48.
21. Viechtbauer W. Conducting meta-analyses in R with the metafor package. *J Stat Softw.* 2010;36(3):1–48.
22. Wallace BC, Dahabreh IJ, Trikalinos TA, Lau J, Trow P, Schmid CH. Closing the gap between methodologists and end-users: R as a computational back-end. *J Stat Softw*. 2012;49(5):1–15.
23. Wan X, Wang W, Lui J, Tong T. Estimating the sample mean and standard deviation from the sample size, median, range and/or interquartile range. *BMC Med Res Methodol*. 2014;14:135.
24. Lee KF, Chong CN, Wong J, Cheung YS, Wong J, Lai P. Long-term results of laparoscopic hepatectomy versus open hepatectomy for hepatocellular carcinoma: a case-matched analysis. *World J Surg*. 2011;35(10):2268–74.
25. Xiao L, Xiang L-J, Li J-W, Chen J, Fan Y-D, Zheng S-G. Laparoscopic versus open liver resection for hepatocellular carcinoma in posterosuperior segments. *Surg Endosc.* 2015;29(10):2994–3001.
26. Hu B-S, Chen K, Tan HM, Ding X-M, Tan JW. Comparison of laparoscopic vs open liver lobectomy (segmentectomy) for hepatocellular carcinoma. *World J Gastroenterol*. 2011;17(42):4725–8.
27. Ker CG, Chen JS, Kuo KK, Chuang SC, Wang SJ, Chang WC et al. Liver surgery for hepatocellular carcinoma: laparoscopic versus open approach. *Int J Hepatol.* 2011;2011:596792.
28. Aldrighetti L, Guzzetti E, Pulitanò C, Cipriani F, Catena M, Paganelli M et al. Case-matched analysis of totally laparoscopic versus open liver resection for HCC: short and middle term results. *J Surg Oncol.* 2010;102(1):82–6.
29. Endo Y, Ohta M, Sasaki A, Kai S, Eguchi H, Iwaki K et al. A comparative study of the long-term outcomes after laparoscopy-assisted and open left lateral hepatectomy for hepatocellular carcinoma. *Surg Laparosc Endosc Percutan Tech.* 2009;19(5):e171–4.
30. Zhang Y, Huang J, Chen X-M, Sun D-L. A comparison of laparoscopic versus open left hemihepatectomy for hepatocellular carcinoma. *Surg Laparosc Endosc Percutan Tech.* 2016;26(2):146–9.
31. Ahn KS, Kang KJ, Kim YH, Kim T-S, Lim TJ. A propensity score-matched case-control comparative study of laparoscopic and open liver resection for hepatocellular carcinoma. *J Laparoendosc Adv Surg Tech*. 2014;24(12):872–7.
32. Kim H, Suh K-S, Lee K-W, Yi N-J, Hong G, Suh S-W et al. Long-term outcome of laparoscopic versus open liver resection for hepatocellular carcinoma: a case-controlled study with propensity score matching. *Surg Endosc.* 2014;28(3):950–60.
33. Truant S, Bouras AF, Hebbar M, Boleslawski E, Fromont G, Dharancy S et al. (2011) Laparoscopic resection vs. open liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: a case-matched study. *Surg Endosc.* 25(11):3668–77.
34. Laurent A, Cherqui D, Lesurtel M, Brunetti F, Tayar C, Fagniez PL. Laparoscopic liver resection for subcapsular hepatocellular carcinoma complicating chronic liver disease. *Arch Surg.* 2003;138(7):763–9. **(discussion 769)**.
35. Zhang J, Zhou Z-G, Huang Z-X, Yang K-L, Chen J-C, Chen J-B et al. Prospective, single-center cohort study analyzing the efficacy of complete laparoscopic resection on recurrent hepatocellular carcinoma. *Chin J Cancer*. 2016;35(1):25.
36. Luo L, Zou H, Yao Y, Huang X. Laparoscopic versus open hepatectomy for hepatocellular carcinoma: short- and long-term outcomes comparison. *Int J Clin Exp Med.* 2015;8(10):18772–8.
37. Beppu T, Hayashi H, Okabe H, Imai K, Nitta H, Masuda T et al. Hybrid-including endoscopic versus open hepatic resection for patients with hepatocellular carcinoma meeting the Milan criteria: a propensity case-matched analysis. *Anticancer Res.* 2015;35(3):1583–90.
38. Cheung TT, Poon RTP, Dai WC, Chok KSH, Chan SC, Lo CM. Pure Laparoscopic versus open left lateral sectionectomy for hepatocellular carcinoma: a single-center experience. *World J Surg*. 2016;40(1):198–205.
39. Yamashita Y-I, Ikeda T, Kurihara T, Yoshida Y, Takeishi K, Itoh S et al. Long-term favorable surgical results of laparoscopic hepatic resection for hepatocellular carcinoma in patients with cirrhosis: a single-center experience over a 10-year period. *J Am Coll Surg*. 2014;219(6):1117–23.
40. Memeo R, de'Angelis N, Compagnon P, Salloum C, Cherqui D, Laurent A et al. (2014) Laparoscopic vs. open liver resection for hepatocellular carcinoma of cirrhotic liver: a case–control study. *World J Surg*. 38(11):2919–26.
41. Kanazawa A, Tsukamoto T, Shimizu S, Kodai S, Yamazoe S, Yamamoto S et al. Impact of laparoscopic liver resection for

hepatocellular carcinoma with F4-liver cirrhosis. *Surg Endosc*. 2013;27(7):2592–7.

42. Cheung TT, Poon RTP, Yuen WK, Chok KSH, Jenkins CR, Chan SC et al. Long-term survival analysis of pure laparoscopic versus open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a single-center experience. *Ann Surg*. 2013;257(3):506–11.
43. Kobayashi S, Nagano H, Marubashi S, Kawamoto K, Wada H, Eguchi H et al. Hepatectomy based on the tumor hemodynamics for hepatocellular carcinoma: a comparison among the hybrid and pure laparoscopic procedures and open surgery. *Surg Endosc*. 2013;27(2):610–7.
44. Belli G, Fantini C, D'Agostino A, Cioffi L, Langella S, Russolillo N et al. Laparoscopic versus open liver resection for hepatocellular carcinoma in patients with histologically proven cirrhosis: short- and middle-term results. *Surg Endosc*. 2007;21(11):2004–11.
45. Kaneko H, Takagi S, Otsuka Y, Tsuchiya M, Tamura A, Katagiri T et al. Laparoscopic liver resection of hepatocellular carcinoma. *Am J Surg*. 2005;189(2):190–4.
46. Shimada M, Hashizume M, Maehara S, Tsujita E, Rikimaru T, Yamashita Y et al. Laparoscopic hepatectomy for hepatocellular carcinoma. *Surg Endosc*. 2001;15(6):541–4.
47. Komatsu S, Brustia R, Goumard C, Perdigao F, Soubrane O, Scatton O. Laparoscopic versus open major hepatectomy for hepatocellular carcinoma: a matched pair analysis. *Surg Endosc*. 2016;30(5):1965–74.
48. Cho JY, Han H-S, Yoon Y-S, Choi Y, Lee W. Outcomes of laparoscopic right posterior sectionectomy in patients with hepatocellular carcinoma in the era of laparoscopic surgery. *Surgery*. 2015;158(1):135–41.
49. Kim S-J, Jung H-K, Lee DS, Yun SS, Kim HJ. The comparison of oncologic and clinical outcomes of laparoscopic liver resection for hepatocellular carcinoma. *Ann Surg Treat Res*. 2014;86(2):61–7.
50. Ai J-H, Li J-W, Chen J, Bie P, Wang S-G, Zheng S-G. Feasibility and safety of laparoscopic liver resection for hepatocellular carcinoma with a tumor size of 5–10 cm. *PLoS ONE*. 2013;8(8):e72328.
51. Kim HH, Park EK, Seoung JS, Hur YH, Koh YS, Kim JC et al. Liver resection for hepatocellular carcinoma: case-matched analysis of laparoscopic versus open resection. *J Korean Surg Soc*. 2011;80(6):412–9.
52. Nguyen KT, Marsh JW, Tsung A, Steel JJL, Gamblin TC, Geller DA. Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal. *Arch Surg*. 2011;146(3):348–56.
53. Tranchart H, Di Giuro G, Lainas P, Roudie J, Agostini H, Franco D et al. Laparoscopic resection for hepatocellular carcinoma: a matched-pair comparative study. *Surg Endosc*. 2010;24(5):1170–6.
54. Lai ECH, Tang CN, Ha JPY, Li MKW (2009) Laparoscopic liver resection for hepatocellular carcinoma: ten-year experience in a single center. *Arch Surg*. 144(2):143–7. **(discussion 148)**.
55. Takahara T, Wakabayashi G, Beppu T, Aihara A, Hasegawa K, Gotohda N et al. Long-term and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study. *J Hepatobiliary Pancreat Sci*. 2015;22(10):721–7.
56. Han H-S, Shehta A, Ahn S, Yoon Y-S, Cho JY, Choi Y. Laparoscopic versus open liver resection for hepatocellular carcinoma: case-matched study with propensity score matching. *J Hepatol*. 2015;63(3):643–50.
57. Lee JJ, Conneely JB, Smoot RL, Gallinger S, Greig PD, Moulton C-A et al. Laparoscopic versus open liver resection for hepatocellular carcinoma at a North-American Centre: a 2-to-1 matched pair analysis. *HPB (Oxford)*. 2015;17(4):304–10.
58. Abu HM. Why do we need guidelines in laparoscopic liver surgery? HPB (Oxford). 2017;19(4):287–8.
59. Katz SC, Shia J, Liau KH, Gonen M, Ruo L, Jarnagin WR et al. Operative blood loss independently predicts recurrence and survival after resection of hepatocellular carcinoma. *Ann Surg*. 2009;249(4):617–23.
60. Kooby DA, Stockman J, Ben-Porat L, Gonen M, Jarnagin WR, DeMatteo RP et al. Influence of transfusions on perioperative and long-term outcome in patients following hepatic resection for colorectal metastases. *Ann Surg*. 2003;237(6):860–9. **(discussion 869–70)**.
61. Twaij A, Pucher PH, Sodergren MH, Gall T, Darzi A, Jiao LR. Laparoscopic vs open approach to resection of hepatocellular carcinoma in patients with known cirrhosis: systematic review and meta-analysis. *World J Gastroenterol*. 2014;20(25):8274–81.
62. Hozo SP, Djulbegovic B, Hozo I. Estimating the mean and variance from the median, range, and the size of a sample. *BMC Med Res Methodol*. 2005;5:13.

APPENDIX 1

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	

PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	

APPENDIX 2

SIGN	**Methodology Checklist 4: Case-control studies**		
Study identification (*Include author, title, year of publication, journal title, pages*)			
Guideline topic:		Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper really a case-control study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist.

Reason for rejection: Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Section 1: Internal validity

In an well conducted case control study:		***Does this study do it?***	
1.1	The study addresses an appropriate and clearly focused question.	Yes Can't say	No
Selection of subjects			
1.2	The cases and controls are taken from comparable populations.	Yes Can't say	No
1.3	The same exclusion criteria are used for both cases and controls.	Yes Can't say	No
1.4	What percentage of each group (cases and controls) participated in the study?	Cases: Controls:	
1.5	Comparison is made between participants and non-participants to establish their similarities or differences.	Yes Can't say	No
1.6	Cases are clearly defined and differentiated from controls.	Yes Can't say	No
1.7	It is clearly established that controls are non-cases.	Yes Can't say	No
ASSESSMENT			
1.8	Measures will have been taken to prevent knowledge of primary exposure influencing case ascertainment.	Yes Can't say	No Does not apply
1.9	Exposure status is measured in a standard, valid and reliable way.	Yes Can't say	No
CONFOUNDING			
1.10	The main potential confounders are identified and taken into account in the design and analysis.	Yes Can't say	No

STATISTICAL ANALYSIS			
1.11	Confidence intervals are provided.	Yes	No
Section 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) ▫ Acceptable (+) ▫ Unacceptable – reject 0 ▫	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes Can't say	No
2.3	Are the results of this study directly applicable to the patient group targeted by this guideline?	Yes	No
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above..		

APPENDIX 3

SIGN

Methodology Checklist 3: Cohort studies

Study identification (*Include author, title, year of publication, journal title, pages*)

Guideline topic:	Key Question No:	Reviewer:

Before completing this checklist, consider:

1. Is the paper really a cohort study? If in doubt, check the study design algorithm available from SIGN and make sure you have the correct checklist.
2. Is the paper relevant to key question? Analyse using PICO (Patient or Population Intervention Comparison Outcome). IF NO REJECT (give reason below). IF YES complete the checklist..

Reason for rejection: 1. Paper not relevant to key question ☐ 2. Other reason ☐ (please specify):

Please note that a retrospective study (ie a database or chart study) cannot be rated higher than +.

Section 1: Internal validity

In a well conducted cohort study:		***Does this study do it?***	
1.1	The study addresses an appropriate and clearly focused question.	Yes ▫ Can't say ▫	No ▫
Selection of subjects			
1.2	The two groups being studied are selected from source populations that are comparable in all respects other than the factor under investigation.	Yes ▫ Can't say ▫	No ▫ Does not apply ▫
1.3	The study indicates how many of the people asked to take part did so, in each of the groups being studied.	Yes ▫	No ▫ Does not apply ▫
1.4	The likelihood that some eligible subjects might have the outcome at the time of enrolment is assessed and taken into account in the analysis.	Yes ▫ Can't say ▫	No ▫ Does not apply ▫
1.5	What percentage of individuals or clusters recruited into each arm of the study dropped out before the study was completed.		
1.6	Comparison is made between full participants and those lost to follow up, by exposure status.	Yes ▫ Can't say ▫	No ▫ Does not apply ▫

ASSESSMENT			
1.7	The outcomes are clearly defined.	Yes ▫ Can't say ▫	No ▫
1.8	The assessment of outcome is made blind to exposure status. If the study is retrospective this may not be applicable.	Yes ▫ Can't say ▫	No ▫ Does not apply ▫
1.9	Where blinding was not possible, there is some recognition that knowledge of exposure status could have influenced the assessment of outcome.	Yes ▫ Can't say ▫	No ▫ ▫
1.10	The method of assessment of exposure is reliable.	Yes ▫ Can't say ▫	No ▫
1.11	Evidence from other sources is used to demonstrate that the method of outcome assessment is valid and reliable.	Yes ▫ Can't say ▫	No ▫ Does not apply▫
1.12	Exposure level or prognostic factor is assessed more than once.	Yes ▫ Can't say ▫	No ▫ Does not apply ▫
CONFOUNDING			
1.13	The main potential confounders are identified and taken into account in the design and analysis.	Yes ▫ Can't say ▫	No ▫
STATISTICAL ANALYSIS			
1.14	Have confidence intervals been provided?	Yes ▫	No ▫
Section 2: OVERALL ASSESSMENT OF THE STUDY			
2.1	How well was the study done to minimise the risk of bias or confounding?	High quality (++) ▫ Acceptable (+) ▫ Unacceptable – reject 0	
2.2	Taking into account clinical considerations, your evaluation of the methodology used, and the statistical power of the study, do you think there is clear evidence of an association between exposure and outcome?	Yes Can't say	No
2.3	Are the results of this study directly applicable to the patient group targeted in this guideline?	Yes ▫	No ▫
2.4	**Notes.** Summarise the authors conclusions. Add any comments on your own assessment of the study, and the extent to which it answers your question and mention any areas of uncertainty raised above.		

APPENDIX 4

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Sposito C, Battiston C, Facciorusso A, Mazzola M, Muscarà C, Scotti M, et al. **Propensity score analysis of outcomes following laparoscopic or open liver resection for hepatocellular carcinoma**	2016	British Journal of Surgery	Laparoscopic surgery in HCC

Study type	Specifications on study design	Study Group		Control Group	Notes	Study quality
		Patients	Cases			
– Case-control	– Retrospective – Single centre – Comparative – Non-randomized	269	43	226 (43 after propensity score matching)	– Patients who underwent only minor liver resections – Initially the two groups were different statistically for some patient and tumor characteristics. To overcome this unavoidable selection bias, 1:1 propensity score matching was applied.	• **++ High quality** • + Acceptable • - Low quality

To compare in a retrospective cohort of patients who underwent liver resection for HCC short- and long-term outcomes of patients undergoing a LLR vs OLR and to analyze the factors related to the risk of developing postoperative complications (Dindo-Clavien classification).

Limitations: After Propensity Score matching the "d" values between groups showed no variable qualifying as unbalanced, with the exception of bilobar tumour distribution, which was more frequent in the LLR than in the OLR (7 versus 1; p=0.151, d=0.76). Relatively small sample size and the absence of randomization limit the strength of the results. Limitation of 1:1 matching because many control subjects (OLR) not matched to treated subjects (LLR) are excluded from the analysis, which can lead to loss information.

Conclusions: Laparoscopic minor liver resections for HCC improved short-term outcomes (lower complication rate and shorter hospital stay in LLR) with similar survival results. The only independent predictor of relevant postoperative complications was the use of laparoscopy (OR=0,12; 95% CI [0.03-0.55] p=0.006). After PSM no difference was found between the OLR and LLR groups with respect to long-term outcomes (overall survival and disease-free survival).

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Vitali GC, Laurent A, Terraz S, Majno P, Buchs NC, Rubbia-Brandt L, et al. **Minimally invasive surgery versus percutaneous radio frequency ablation for the treatment of single small (≤3 cm) hepatocellular carcinoma: a case-control study.**		2016		Surg Endosc		Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Retrospective – Single centre – Comparative – Non-randomized	105	43	45 HCC underwent MIS	– Patients in RFA group showed worse liver synthetic function with lower albumin and higher bilirubin serum levels, and higher ASA scores. – Only patients with CP class A or B biopsy-proven cirrhosis were included and to homogenize the population, patients with a single, 1-3 cm HCC were selected.	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this case control study was to compare RFA with MIS for the management of patients with single ≤3 cm HCCs.

Limitations: Patients underwent RFA demostrated worse liver synthetic function with lower albumin and higher bilirubin levels and also tended to have more comorbidities as ASA score 3. This is a retrospective study and non-randomized.

Conclusions: The rate of complications were similar in both groups. The median hospital stay was 6 (1–16) days in the MIS group versus 1 day (range 1–12 days) in the RFA group (p=0.001). After a median follow-up of 26 (2–129) months, a local tumor progression was detected in 11.7 % (7/60) of patients in the RFA group, while no MIS patient had a local recurrence (p = 0.056). Overall survival was significantly higher in the MIS group (p=0.042).

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Komatsu S, Brustia R, Goumard C, Perdigao F, Soubrane O, Scatton O. **Laparoscopic versus open major hepatectomy for hepatocellular carcinoma: a matched pair analysis.**				2016	Surgical Endoscopy	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Retrospective – Single centre – Comparative – Non-randomized	76	38 (10 left, 28 right)	38 (10 left, 28 right) Matching 1:1	– Intention-to-treat analysis. – Very small sample. – High rate of conversion – Significantly larger maximal tumour size in the open group	• ++ High quality • **+ Acceptable** • - Low quality

This study analyzed the short- and long-term outcomes of Laparoscopic Major hepatectomy for HCC compared with open hepatectomy.

Limitations: The study has a very small sample. Selection bias, there is a significantly larger maximal tumour size in the open group. This is an intention-to-treat analysis; for this reason, all 12 converted cases in the laparoscopic group were analysed as laparoscopic cases. They tried to do a subset analysis, but we think that the sample is so small to get strong conclusion.

Conclusions: the present study demonstrates the technical feasibility as well as superior short-term and comparable oncological outcomes of LMH for HCC compared with the open procedure. The overall complication rates were significantly higher in the open group (23 of 38 (65%)) than in laparoscopic group (12 of 38(31.6%)) p=0.011. The laparoscopic group showed a trend towrd shorter, although not statiscally significant, lengths of postoperative hospital stay (p=0.079). In long-term disease free and overall survival rates of two groups with a median follow-up of 24.7 months showed no significant difference at 3 year between both.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Tokuji Ito, Shogo Tanaka, Shuji Iwai, Shigekazu Takemura, Atsushi Hagihara, Sawako Uchida-Kobayashi, Hiroji Shinkawa,Takayoshi Nishioka, Norifumi Kawada and Shoji Kubo. **Outcomes of laparoscopic hepatic resection versus percutaneous radiofrequency ablation for hepatocellular carcinoma located at the liver surface: A case-control study with propensity score matching.**				2016	Hepatology Research	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Case-control – Retrospective – Non-randomized – Comparative	76	40 patients who underwent LH (27 after PSM)	52 patients who underwent P-RFA (27 after PSM) Matching 1:1	– To compare the short-term outcome of patients with surface HCC who underwent LH with those who underwent P-RFA. – Matched at a ratio 1:1 according to propensity scores.	• **++ High quality** • + Acceptable • - Low quality

Case control Study with Propensity Score Matching (1:1-27:27) Patients with surface HCC treated by laparoscopic resection vs percutaneous RFA.

Limitations: In this study all tumours were located at the liver surface and were small size (in both groups). The total number of patients was relatively small in both groups.

Conclusions: In the Laparoscopic group the duration of hospitalization was longer than in the radiofrequency ablation (12.6 vs 7.6 days, $p < 0.01$). The incidence of local recurrence was lower in the LH group (0%) than in the p-RFA group (8 patients (30%), $p=0.004$) even after PSM. LH is an effective treatment for surface HCC with regard to control of local recurrence.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Zhang Y, Huang J, Chen X-M, Sun D-L. **A Comparison of Laparoscopic Versus Open Left Hemihepatectomy for Hepatocellular Carcinoma**				2016	Surgical Laparoscopy Endoscopy & Percutaneous Techniques	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Case-control – Retrospective – Non-randomized – Comparative	45	20 (laparoscopic)	25 (open)	– To compare the short-term outcome of patients underwent left hemihepatectomy for HCC. Two groups. Open resection vs laparoscopic	• ++ High quality • **+ Acceptable** • - Low quality

Retrospective Case control study in patients with HCC underwent left hemihepatectomy, open Vs laparoscopic resection. The objectives were to evaluate and compare the safety and preioperative and short-term outcomes of laparoscopic Vs open.

Limitations: All results are expressed as median and range values. Very small sample. A short follow up (1 years).

Conclusions: Laparoscopic resection requires a great deal of experience by HPB surgeons, this approach is deemed safe for malignant liver lesions with oncological results comparable to that of open surgery. It offers better short-term results including a shorter hospital stay (7±1 vs 12±2 d; $p<0.05$), less postoperative pain, and lower complication rates ($p<0.01$), no differences in term on oncological resection and less blood loss for the Laparoscopic group ($p<0.05$).

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Lai ECH, Tang CN. **Long-term Survival Analysis of Robotic Versus Conventional Laparoscopic Hepatectomy for Hepatocellular Carcinoma: A Comparative Study.**				2016	Surgical Laparoscopy Endoscopy & Percutaneous Techniques	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Case-control – Prospective – Non-randomized – Comparative – Historical Cohort	413	100 (robotic)	35 (laparoscopic)	– To compare the long-term oncological outcomes of robotis and conventional laparoscopic hepatectomy for HCC	• ++ High quality • **+ Acceptable** • - Low quality

Prospective Case control study in patients with HCC underwent laparoscopic Vs robotic resection..

Limitations: In the robotic group there is a significant higher proportion of major hepatectomies and tumours located at or across posterosuperior segments than conventional laparoscopic group. The groups of patients are maden in difference time of the study (since 1998 to 2015), laparoscopic group at the beginning.

Conclusions: There was no difference in overall morbidity rate and operative mortality rate between both groups. Both groups had no mortality. There was no difference between the 2 groups in R0 resection rate, long-term overall survival and disease-free survival after mean follow up of 61.6 months. This study is the largest study comparing robotic vs laparoscopic partial hepatectomy. Robotics surgery may have an impact on therapeutic strategy of HCC.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

LAI C, Jin R-A, Liang X, Cai XJ. **Comparison of laparoscopic hepatectomy, percutaneous radiofrequency ablation and open hepatectomy in the treatment of small hepatocellular carcinoma**				2016	Journal of Zhejiang University-SCIENCE B (Biomedicine & Biotechnology)	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Case-control – Prospective – Non-randomized – Comparative	94	28 (lap) 33 (open)	33 (p-RFA) Patients were matched by age, sex, CPC, HCV, HBV, cirrhosis status and preoperative laboratory results.	– Null hypothesis: LH, OH and p-RFA provided similar prognostic outcomes and survival rates for patients with small HCC (Milan criteria).	• ++ High quality • **+ Acceptable** • - Low quality

Prospective Cohort study where compare 3 groups (resection by open or laparoscopic surgery and p-RFA).

Limitations: The patients in the p-RFA groups were older and the tumour size was smaller than in the other groups. Bias may exist in the treatment selection based on the patient's age, their intension-ti-treat wishes and the tumour status.

Conclusions: For small HCC patients radical resections including OH and LH offer better survival results than p-RFA. Laparoscopic surgery shared similar curative effects with OH in terms of both disease-free survival and 3-year overall survival. Minimally invasive surgery should be recommended in younger patients with small HCC, while elderly patients may choose either liver resection or RFA.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Chang SK, Tay CW, Shen L, Iyer SG, Kow AW, Madhavan K. **Long-Term Oncological Safety of Minimally Invasive Hepatectomy in Patients with Hepatocellular Carcinoma: A Case- Control Study. Ann Acad Med Singap**				2016	Ann Acad Med Singap	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Case-control – retrospective – Non-randomized – Comparative	60	30 (LR)	30 (OR)	– Matching for extent of tumour resection, age nad cirrhosis status.	• ++ High quality • **+ Acceptable** • - Low quality

This Case control retrospective study comparing the short and long-term oncological safety of HCC patients who underwent Minimally invasive hepatectomy and open hepatectomy.

Limitations: Retrospective. Non-randomized study.

Conclusions: The mean blood loss during surgery was significantly lower in LR (p=0.04). Hospitalization is significantly shorter in LR (p=0.04). The survival (p=0.18) and disease-free survival rate (p=0.41) were similar in both groups. Laparoscopic resection is a safe and feasible curative treatment option for HCC with similar oncological outcomes compared to open resection.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC? What is the role of LLR in cirrhotic patients?

Shehta A, Han H-S, Yoon Y-S, Cho JY, Choi Y. **Laparoscopic liver resection for hepatocellular carcinoma in cirrhotic patients: 10-year single-center experience.**				2016	Surg Endosc	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Retrospective – Single centre – Non randomized – Comparative	389	141 liver cirrhotic (LC)	91 Non-LC	– Patients were divided into two groups according to the status of their liver parenchyma, with and without liver cirrhosis (LC). LC group with histologically confirmed F4 cirrhosis.	• **++ High quality** • + Acceptable • - Low quality

The aim of this study was to evaluate our experience of LLR for HCC and to compare perioperative and long-term outcomes between patients with and without liver cirrhosis.

Limitations: Minor resection were more performed in LC group and showed a smaller median tumor size and smaller resection margin. Retrospective and non randomized study.

Conclusions: More minor resection were done in LC group (p=0.011). There were no statistically significant differences between the two groups regarding operation time, blood loss, transfusión requiriments and intraoperative complications. The non-LC group had a significantly larger resection margin than did the LC group [LC, 0.8 cm (0.01–6.5); non-LC, 1.3 cm (0.1–6.8); p = 0.019]. There were no statistically significant differences between groups in terms of recurrence pattern and overall survival. In conclusion, the current study demonstrated that LLR for HCC is feasible in patients with cirrhosis. LLR in cirrhotic patients showed comparable results to non-cirrhotic patients in terms of perioperative and long-term outcomes.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Cheung TT, Poon RTP, Dai WC, Chok KSH, Chan SC, Lo CM. **Pure Laparoscopic Versus Open Left Lateral Sectionectomy for Hepatocellular Carcinoma: A Single Center Experience.**				2016	World Journal of surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Case-control – Retrospective designed with prospective collection of patients' data. – Non-randomized – Comparative	967	24	29 open (matching on tumour characteristics and liver functions)	– To analyse the survival outcome of laparoscopic left lateral sectionectomy compared to open approach in patients with HCCs.	• **++ High quality** • + Acceptable • - Low quality

This study was the first report on laparoscopic left lateral sectionectomy with HCCs and liver cirrhosis.

Limitations. It is a good study with an adecaute statistical methodology. Maybe a limitation could be the small number of patients (they use median and range-no gaussian distribution) and the retrospective character.

Conclusion: The laparoscopic group had a median blood loss of 100 ml while the open group ha d a median of 300 ml ($p<0.001$). Less blood loss is observed in laparoscopic group even in the presence of liver cirrhosis.

They do a subgroup analysis in patients with cirrhosis (F4) in which the amount of bleeding is significantly lower in the laparoscopy group being tumor characteristics and resection margins similar ($p>0.05$).

There are no significant differences in terms of survival and disease-free survival in both groups at 1 year, 3 years and 5 years.. Laparoscopic left lateral sectionectomy is a safe procedure due to the advancement of technology and accumulating experience. Its simplicity, repeatability, and association with less blood loss makes it a good option for patient with HCC and cirrhosis.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Zhang J, Zhou Z-G, Huang Z-X, Yang K-L, Chen J-C, Chen J-B, et al. **Prospective, singlecenter cohort study analyzing the efficacy of complete laparoscopic resection on recurrent hepatocellular carcinoma.**				2016	Chinese Journal of Cancer	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Cohorts – Prospective – Non randomized – Single-centre	64	31 (LR)	33 (OR)	– Inclusion criteria: Recurrent HCC, recurrent in left or right lobe without noteworthy surgical contraindications, no major vessel or bile duct tumor invasion or metastasis, Grade A or B liver function or grade C. – Exclusion criteria: major vessel or bile duct tumor invasion, recurrent HCC located in right liver parenchyma and near secondary vessels and bile ducts, extrahepatic metastasis, grade C liver function, noteworthy surgical contraindication.	• ++ High quality • **+ Acceptable** • - Low quality

This study examined the treatment of recurrent HCC in patients who received a prior hepatectomy.

Limitations. Small number of patients. No randomized study. With a sample size so small subgroup analysis does not have a good statistical power.

Conclusion: Significant differences were observed between the LR (shorter) and OR (p=0.031), intraabdominal blood loss (p=0.012), postoperative time until the patient could walk (p=0.004), anal exsufflation time (p=0.041), VAS scores (p<0.001), postoperative hepatic function (p<0.05) and length of hospital stay (p=0.014) were better in lap group than open group. Subgroup analysis in the lap group compared patients with ipsilateral recurrence with contralateral recurrence. The last one tended to have less intraoperative blood loss (p=0.012) and a shorter hospital stay (p=0.021). No significant difference was observed in relapse-free survival between the two groups.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC? What is the role of LLR in cirrhotic patients?

Takahara T, Wakabayashi G, Nitta H, Hasegawa Y, Katagiri H, Takeda D, et al. **Laparoscopic liver resection for hepatocellular carcinoma with cirrhosis in a single institution**.				2015	Hepatobiliary Surgery and Nutrition	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Retrospective – Single centre – Comparative – Non-randomized	118 (LLR)	60 (NLC-LLR)	58 (LC-LLR)	– Inclusion criteria for LLR were a tumor size of less than 10 cm and the absence of severe adhesions, invasión to major vessels, or a need for vessel reconstruction. – One of the major obstacles ofLLR in cirrhotic patients is the risk of massive bleeding, because these patients have a bleeding tendency related to primary hemostasis dysfunction	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this retrospective study was to compare the feasibility and safety of LLR for HCC between non-liver cirrosis and liver cirrosis patients at a single high volumen laparoscopy center.

Limitations: Wedge resections were mainly performed in the LC-LLR group. Non-randomized study and retrospective and small number of patients.

Conclusions: The tumor size in the LC-LLR was significantly smaller than NLC ($p<0.001$). There were similar surgical margin, incidence of blood loss and transfusión requerements. No significant difference in the complication rate. There was a significantly lower incidence of postoperative ascites in the LC-LLR than in the NLC group. LLR for selected HCC patients with cirrosis is a feasible and promising procedure that is associated with less blood loss and fewer postoperative complications, especially the incidence of postoperative ascites.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Leong WQ, Ganpathi IS, Kow AWC, Madhavan K, Chang SKY. **Comparative study and systematic review of laparoscopic liver resection for hepatocellular carcinoma.**				2015	World Journal of Hepatology	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Systematic review and – Comparative study in their hospital	– Case-control – Retrospective – Non-randomized – Systematic review of comparative studies (17 high-quality studies)	152	42 laparoscopic resection	110 open resection		• **++ High quality** • + Acceptable • - Low quality

This study is a systematic review and comparative study of patients who underwent open vs laparoscopic liver resection for HCC. Comparative study use 152 patients (42 laparoscopic and 110 open surgery). A total of 17 studies published between 2001 and 2014 were identified as eligible for analysis using Forest plots.

Limitations. In the comparative study with 152 patients there are several selection bias. In lap groups the tumour size is bigger than in the open group. The ASA score is higher in the open group and has more patients with microscopic vascular invasión.For this reason is possible that the disease free survival rate was higher in the open group.

In the systematic review one important limitation is that all comparative studies including are non-randomized controlled studies (retrospective or retrospective matched).

Conclusion: The systematic review and comparative study show that as a curative treatment for HCC, LLR provides better short-term outcomes than OLR in terms of intraoperative blood loss, blood transfusions and length of hospital stay, while both LLR and OLR provide similar long-term oncologic outcomes.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Li W, Zhou X, Huang Z, Zhang H, Zhang L, Shang C, et al. **Laparoscopic surgery minimizes the release of circulating tumor cells compared to open surgery for hepatocellular carcinoma.**				2015	Surg Endosc	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Prospective cohorts	– Cohorts – Prospective – Single centre – Randomized	26	12 (LR)	14 (OR)	– Inclusion criteria: Compensated cirrhosis or noncirrhotic liver, platelet count of 100x109/l or higher, and a tumor location that was not in contect with the portal pedicle or hepatic veins. – Exclusion criteria: distant metastases, ASA>3 and age>80 years, patients who underwent intraoperative blood transfusion.	• **++ High quality** • + Acceptable • - Low quality

The aim of this study was to determine whether tumor manipulation enhances cáncer cell reléase from the primary tumor in HCC patients and which surgical approach (OR vs LR) is superior with respect to preventing tumor cells from scattering in the blood.

Limitations: There are some limitations, despite the high sensitivity of this method in detecting CCSCs, the overall detection accuracy did not reach 100 %.They cannot completely exclude the impact of variations in clinical situations, such as individual patient differences. In the study did not investigate which clinical implications have the results obtained in patients, as recurrence or survival.

Conclusions: The two groups presented a homogeneous distribution in the characteristics and potential confounders. The IL-6, IL-8 and TNF levels were similar between groups before the operation. The mean increases in the POD serum levels of IL-6 and IL-8 in the LR group were significantly less than those in the OR group. Only the IL-6 levels in the LR showed a significantly diminished increase 24 h after surgery compared to OR.

No signinficant difference was found in the level of CCSCs between the two groups before surgery manipulation. There was a trend toward an increased level of CCSCs in the two groups after tumor resection, and a comparison of the median levels revealed a significantly lower increase (P = 0.041) following laparoscopic surgery compared to open surgery. Seems to be clear that the level of CCSCs was affected by the nature of the surgical intervention being applied.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Xiao L, Xiang L-J, Li J-W, Chen J, Fan Y-D, Zheng S-G. **Laparoscopic versus open liver resection for hepatocellular carcinoma in posterosuperior segments**				2015	Surg Endosc	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control study	– Case control – Retrospective – Non-randomized – Single centre	127	41 (LR)	86 (OR)	– Inclusion criteria: Diagnosis of HCC, solitary lesion (8 cm or less), located posterosuperior segment, no satellite lesions or intrahepatic metastases and no blood vessel or bile duct invasion, Child-Pugh A or B, ICG≤15%, no tumor rupture or bleeding and no severe adhesions in the surgical field.	• **++ High quality** • + Acceptable • - Low quality

This study was designed to compare the short-term efficacy and survival of patients with HCC, particularly when combined with cirrhosis, who underwent LLR and OLR of the posterosuperior segments.

Limitations: The optimal distance of the surgical margin for malignant tumors has not been determinated, althougn studies have suggested that if negative margins are ensured, this distance does not have a significant effect on tumor recurrence. Retrospective study and non-randomized.

Conclusions: Intraoperative blood loss was significantly lower and postoperative hospital stay significantly shorter in the LLR than in the OLR group. The overall complication rates were significantly lower in the LR than in OR (p=0.021). Overall survival rate and disease-free survival rate were similar in both groups.

LR for selected patients with HCC in the posterosuperior segments may offer the same oncologic outcomes as conventional procedures, while being associated with such advantages as lower blood loss, fewer postoperative complications and shorter hospital stay.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Takahara T, Wakabayashi G, Beppu T, Aihara A, Hasegawa K, Gotohda N, et al. **Longterm and perioperative outcomes of laparoscopic versus open liver resection for hepatocellular carcinoma with propensity score matching: a multi-institutional Japanese study.**				2015	Journal of Hepato-Biliary-Pancreatic Sciences	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Case control – Retrospective – Multicentre – One to one propensity case-matched analysed	3405	436 (LR) after PSM=387	2969 (OR) after PSM=387	– The PSM were generated with sex, age, underlying liver disease, tumor size, number, AFP, ICGR 15 min, extent of liver damage (CLCSGJ), Child-Pugh Score, difficult tumor location and distant metastasis.	• **++ High quality** • + Acceptable • - Low quality

The aim of this study was to compare the long term outcomes and perioperative outcomes of LR with those of OR for HCC between well-Matched patient groups.

Limitations: This study after PSM included a small number of patients. Non-randomized and retrospective.

Conclusions: In LR the median blood loss was significantly less than in the OR ($p<0.001$), and the median postoperative hospital stay for LR was significantly shorter ($p<0.001$). The operation time was significantly longer in LR ($p=0.025$). Postoperative complication rate in LR were significantly lower ($p=0.003$). There were no significant differences in OS and DFS between the matched groups.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Han H-S, Shehta A, Ahn S, Yoon Y-S, Cho JY, Choi Y. **Laparoscopic versus open liver resection for hepatocellular carcinoma: Case-matched study with propensity score matching.**				2015	Journal of Hepatology	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Case-control – Matching 1:1 – PSM – Retrospective – Single centre	389	232 (LR) (88 after PSM)	157 (88 after PSM)	– The PSM model was generated using baseline variables (Sex, age…), CP score, preoperative laboratory results, liver state, cause of liver cirrhosis, tumor charasteristics, ascites and extend of liver resection.	• **++ High quality** • + Acceptable • - Low quality

The aim of this study is to compare perioperative and long term outcomes of laparoscopic versus open liver resection for HCC between two matched groups.

Limitations: In spite of PSM, there is still possibility that OR is more performed for major and complex cases.

Conclusion: LR showed longer operative time than OR (p=0.07), less use of Pringle manoeuver (p=0.034) and duration (p=0.026), shorter hospital stay (p≤0.001), larger resection margin (p=0.011). There was no difference in the rates of intraoperative complications. Also, the LR group showd statistically significant lower postoperative morbidity (p=0.042). There was no statistical significance between both groups in terms of OS and DFS rates.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Cho JY, Han H-S, Yoon Y-S, Choi Y, Lee W. **Outcomes of laparoscopic right posterior sectionectomy in patients with hepatocellular carcinoma in the era of laparoscopic surgery.**				2015	Surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Case-control – Retrospective – Non-randomized	408	24	19	– Case control study – Very small sample – Not strong results	• ++ High quality • **+ Acceptable** • - Low quality

When determining the extent of liver resection for the treatment of HCC, it is important to achieve a balance between operative curability and preservation of remaining hepatic function. RPS should be considered when it is necessary to preserve the liver's functional reserve. This is a case control study to evaluate the safety of laparoscopic Right Posterior sectionectomy (RPS) in terms of its operative and oncologic outcomes. From 408 patients they analyzed the clinical data of 24 patients who underwent laparoscopic RPS for HCC and compared outcomes with patients who underwent open RPS (n=19).

Limitations: The complex case were not considered for a laparoscopic approach (tumors larger than 5 cm, adjacent to the main portal pedicle or IVC, a central lesions…). The study has a small number of patients.

Conclusions: When compare the two groups the mean operation time was longer in laparoscopy group, there was no difference in the mean resection margin and rate of postoperative complications. The duration of Hospital stay in the LG was shorter but no statistical difference.With a median follow up of 56 months there was no statistical difference in 5 year overall patient survival rate and disease-free survival rate. Therefore, RPS have been regarded as major liver resectio, complexity and wide resection, and we need to have randomized clinical trial comparing open with laparoscopic patients.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Martin RCG, Mbah NA, St Hill R, Kooby D, Weber S, Scoggins CR, et al. **Laparoscopic versus open hepatic resection for hepatocellular carcinoma: improvement in outcomes and similar cost.**				2015	World Journal of Surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Cohorts	– Prospective collected – Multicenter – Cohorts – Comparative	354	100 LR (65 pure lap and 35 hand-assisted)	254	– Financial analysis was restricted to the post-laparoscopic era – Cost was modelled with multivariable linear regression, with adjustments for the year of operation and centre in which the operation was performed. – Analyses depends of the surgical era (2004)	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this study was to compare outcomes of LR vs OR exclusively for HCC regards to morbidity and cost (First study to evaluate cost)

Limitations: There was a signifcant difference in tumor size with larger tumors in the open group (p=0.006). The open group had higher percentage of major hepatectomy. Another limitation of this study is the relatively short median follow-up of 26 months. Non- randomized.

Conclusions: Blood loss was significatly less in LR (p<0.001). The incidence of any complication and 90-day mortality were similar between the two groups, with a similar reoperation rate. Laparoscopic procedures remained independently associated with shorter length of stay in the multivariable model (OR 0.23, 95 % CI 0.06–0.87; p = 0.031). With regards to cost analysis, a comparison of operating room charges for the laparoscopic approach compared to an open technique demonstrated no statistically significant difference. Laparoscopic liver resection for HCC has comparable perioerative outcomes to OR. LR show decreased length of stay after LR and comparable cost between the two procedures.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Xiang L, Xiao L, Li J, Chen J, Fan Y, Zheng S. **Safety and feasibility of laparoscopic hepatectomy for hepatocellular carcinoma in the posterosuperior liver segments.**				2015	World Journal of Surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Retrospective – Case control – Nonrandomized – Single centre – Comparative	126	56 patients posterosuperior segments (I, Via, VII and VIII)	70 patients anterolateral segments (II, III, IVb, V and VI)	– Inclusion criteria: preoperative diagnosis of HCC, good general condition and normal function of vital organs tolerant to hepatectomy, ≤8 cmdiameter solitary lesión, CH score A or B, hepatic reserve capacity (ICGR-15), no tumor ruptura, no preoperative treatment.	• ++ High quality • **+ Acceptable** • - Low quality

The purpose of this study was to investigate the safety and feasibility of LH for the treatment of HCC in posterosuperior liver segments (I, IVa, VII and VIII), especially in association with cirrhosis.

Limitations: The operation time was longer in PS group probably because this segments required full mobilization of the liver and more time to expose the lesión than in AL group. The high levels of enzymes in the 1 and 3 day is because the longer Pringle maneuver in these patients, without any clinical significanceSmall number of patients. Retrospective. Non randomized.

Conclusions: There were statistically significant differences between the two groups of patients in the operation time (217.5 ± 63.7 vs 176.8 ± 48.4 min, P = 0.000), blood loss (295.5 ± 186.8 vs 220.4 ± 164.2 ml, P = 0.001), conversion rate from laparoscopy to laparotomy (17.9 vs 7.1 %, P = 0.031), and transfusion rate (16.1 vs 4.3 %, P = 0.025). The tumor size (P = 0.894) and resection margin of the pathological specimen (P = 0.102) showed no statistically significant differences between the PS and AL group. The postoperative complication rate showed no statiscally significant difference between the PS al AL group (p=0.873). There were not statistically significant differences in terms of survival and disease-free survival rate. These results suggest that the use of LH to treat cirrosis associated HCC was safe, feasible and achieved the same oncological and perioperative outcomes in the PS group as in the AL group.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Lee JJ, Conneely JB, Smoot RL, Gallinger S, Greig PD, Moulton C-A, et al. **Laparoscopic versus open liver resection for hepatocellular carcinoma at a North-American Centre: a 2- to-1 matched pair analysis**				2015	HPB (Oxford)	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control	– Case-control (Matching 1:2) – Retrospective – Comparative	129	43 LLR	86 (OLR)	– To compare the outcomes of HCC patients with LLR vs OLR on a 2-to-1 matched-case basis. – Matching according to age, size and number tumor (risk factor of survival)	• **++ High quality** • + Acceptable • - Low quality

LLR for HCC in comparison to OLR in peri-operative and long term oncológical outcomes are described from a single North American Institution. 43 cases Vs 86 control matched for age, maximal tumour size and number.

Subgroup analysis of the cirrhotic patients shows that there was no statistical difference between the LLR and OLR groups in terms of overall survival and recurrence-free survival.

Limitations: Small simple size. Tehre is a discrepancy in length of follow up between groups (LLR has a shorter follow up thna OLR).

Conclusions: LLR offers significant benefits in term of peri-operative outcomes compared with OLR and suggest that LLR should be considered as a first-line modality. Overall survival appears equivalent after LLR and OLR, however there appears to be a non-significant trend suggesting a potentially higher intra-hepatic recurrence rate after LLR in this series, probably there may be a predilection towards non-anatomic resections in LLR in this group.and because there are more patients with HCV (two factors which are associated with high recurrence rate).

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Beppu T, Hayashi H, Okabe H, Imai K, Nitta H, Masuda T, et al. **Hybrid-including endoscopic versus open hepatic resection for patients with hepatocellular carcinoma meeting the Milan criteria: a propensity case-matched analysis.**				2015	Anticancer Research	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control	– Case control – Matching 1:1 – Propensity socre matching – Non-randomized – Retrospective. – Single centre	269	89 EH (52 after PSM)	180 OH (52 after PSM)	– One to one propensity case-matched analysis was used. – Patients who meeting the Milan criteria with sufficient liver function.	• **++ High quality** • + Acceptable • - Low quality

Patients with HCC who meet the Milan criteria are suitable candidates for EH. This study was undertaken to determine the surgical outcome and long-term prognosis of EH in comparison to those of conventional OH for HCC patients who met the Milan criteria.

Limitations: In the OH groups there were patients with complicated tumor location. The study included relatively small number of patients. Non-randomized. Retrospective.

Conclusions: The median operative time (p=0.049) and the median blood loss (p<0.001) were significantly less with EH than with OH. The morbidity rates were siilar between the two groups. Median postoperative hospital stay was significantly shorter for EH patients than for OH patients (p=0.002). There were no significant differences in DFS (p=0.978) and OS (p=0.614) between the two groups.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Luo L, Zou H, Yao Y, Huang X. **Laparoscopic versus open hepatectomy for hepatocellular carcinoma: short- and long-term outcomes comparison.**				2015	International journal of clinical and experimental medicine	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control	– Retrospective – Case-control-matching 1:1 – Non-randomized – Single centre	106	53	53	– Matching 1:1 – Outcomes short and long-term. – Median follow up 35 months.	• ++ High quality • **+ Acceptable** • - Low quality

Case control study (1:1) matching according for age, gender, liver function, underlying liver disease, type of surgery, and American Society of Anesthesiologists (ASA) class.

Limitations: The patients who required conversión to an open procedure were excluded. Type of surgery. Only easy cases, LLS and subsectionectomy (No added cases of major hepatectomy or posterior segments). The patients were not assigned randomly into the two goups. The mean follow-up time was not very long (median 35 months).

Conclusions: The lap group presented longer operative time, lower blood loss, less pain, lower nedd of analgesic and less hospital recovery time (ss), no differences in the complications were found. Both groups did not have significant differences in overall survival trend and disease-free survival.. However, further randomized studies are required to verify the results.

Guideline topic: HCC-comparative	
CQ	What is the role of LLR in cirrhotic patients?

Chen J, Bai T, Zhang Y, Xie Z-B, Wang X-B, Wu F-X, et al. **The safety and efficacy of laparoscopic and open hepatectomy in hepatocellular carcinoma patients with liver cirrhosis: a systematic review**				2015	International journal of clinical and experimental medicine	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Systematic review – Meta-analysis "intention-to-treat"	– Systematic review (retrospective trials) – Meta-analysis	828	281 LH	547 OH	– NOS was used to assess the risk of bias for quality assessment of non-randomized studies. – The overall quality was good. (NOS score 7 out of 9)	• **++ High quality** • + Acceptable • - Low quality

Systematic review and analysis (Meta-analysis intention-to-treat) the safety and the efficiency of LH in HCC patients with liver cirrhosis. Included 7 retrospective trials with 828 patients. They analyzed the heterogeneitu by calculating i2 and the homogeneity between trials was assessed using X2 test.

Results: In LH: tumor margin was wider (p=0.002), Similar operating time (p=0.2), less blood loss (p=0.03), less blood transfusión (p=0.004), decreased postoperative moribility (p<0.0001), similar postoperative mortality (p=0.48), similar curative resection (p=0.26), shorter hospital stay (p=0.0002).The overall survival at 1 year was similar, but at 5 year in LH seemed to be significaty higher than OH (RR=1.28, 95% CI 1.01 to 1.62, p=0.04, i2 =62%).Similar disease free survival at 1-,3- and 5-years.

Limitations: There is a problema because all the studies included were retrospective, non-randomized; which would increase the selection bias. The simple size is small which decrease the reliability of the final results. The patients in OH had huge HCC, higher degree of cirrhosis, improper location that had high risk of blood loss.(selection bias).

Conclusions: LH may provide better intraoperative and short-term outcomes than OH in HCC patients with liver cirrhosis. However no significant survival benefit was shown between them. But a tendency to have better survival benefit still could be found of LH in HCC patients with liver cirrhosis.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Ahn KS, Kang KJ, Kim YH, Kim T-S, Lim TJ. **A propensity score-matched case-control comparative study of laparoscopic and open liver resection for hepatocellular carcinoma.**				2014	Journal of laparoendoscopic & advanced surgical techniques	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control	– Case control – Retrospective – Nonrandomized – Propensity score matching 1:1	292 (202)	52 (after PSM= 51 LR)	150 (after PSM=51 OR)	– LR was applied to patients with CP class A, without invasion or close to the main portal pedicle or major hepatic veins. – Conversion cases were excluded.	• **++ High quality** • + Acceptable • - Low quality

The purpose of this study was to compare the perioperative and long-term oncologic outcomes of LLR and OLR for single HCC in groups of well-matched patients using PSM.

Limitations: A well-designed prospective study will be needed to affirm the validaty of LR for HCC. Non-randomized. Retrospective.

Conclusions: The postoperative hospital stay period was significantly shorter in the LR (p=0.004). The overall survival and disease-free survival rates were similar between the two groups. LR for HCC is safe, and long-term oncologic outcomes were comparable to those of OR in selected patients.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC? What is the role of LLR in cirrhotic patients?

Yamashita Y-I, Ikeda T, Kurihara T, Yoshida Y, Takeishi K, Itoh S, et al. **Long-term favorable surgical results of laparoscopic hepatic resection for hepatocellular carcinoma in patients with cirrhosis: a single-center experience over a 10-year period.**				2014	Journal American College Surgical	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Case control study – Retrospective – Single centre – Non-randomized	162	63 (LR)	99 (OR)	– Patients with cirrhosis underwent surgery for primary HCC within the Milan Criteria.	• ++ High quality • **+ Acceptable** • - Low quality

They review the long-term surgical results of LR for HCC in patients with cirrhosis over the 10 year period at a single institution compared with OR group.

Limitations: the definition of cirrhotic liver is not clear how and when set it. They did not analyze the type of liver resection on each group to study the homogeneity. LR group tends to be applied for limited resection to peripheral ventral small HCC in which hepatic resections are relatively easy to perform.

Conclusions: The morbidity rate in LR was lower (p=0.045), the positive rate of ascites in LR was lower (p=0.007), the duration of hospital stay in LR was shorter (p=0.0008) than in the OR group. There were no significant difference in DFS (p=0.519) or overall survival (p=0.679) between the two groups. LR for HCC in patients with cirrhosis is associated with less morbidity and shorter hospital stays, with no compromiso in patient survival.

Guideline topic: HCC-comparative	
CQ	What is the role of LLR in cirrhotic patients?

Twaij A, Pucher PH, Sodergren MH, Gall T, Darzi A, Jiao LR. **Laparoscopic vs open approach to resection of hepatocellular carcinoma in patients with known cirrhosis: systematic review and meta-analysis.**				2014	World Journal of Gastroenterology	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Systematic review and Metanalyses	– Meta-analyses – Systematic review (4 studies)	420	150 (LR)	270 (OR)	– The aim was to review the currently available data comparing LR vs OR for HCC in patients with known cirrhosis. – The risk of bias was assessed using NOS with a good quality (7 and 8 out of 9).	• ++ High quality • **+ Acceptable** • - Low quality

All studies included were single centre retrospective cohort studies (case matched).

Limitations: Small number of studies (4) with a lack of randomized trials. In the studies there was no reported in tumour size or patients demographics. Relatively small size of the studies included. For this reason this review had several selection bias.

Conclusions: laparoscopic approach, compared to open surgery, may result in improved short-term outcomes in the form of wider resection margins, reduced intraoperative blood loss and need for transfusions, as well as reduced morbility rates and shorter lengths of stay in cirrhotic liver. No statistically significant difference was reported in both long-term survival and disease-free survival. This study suggests that the advantages of laparoscopy also be apply in patients with know cirrhosis.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC? What is the role of LLR in cirrhotic patients?

Memeo R, de'Angelis N, Compagnon P, Salloum C, Cherqui D, Laurent A, et al. **Laparoscopic vs. Open Liver Resection for Hepatocellular Carcinoma of Cirrhotic Liver: A Case–Control Study.**				2014	World Journal of Surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Case control study – Matching 1:1 – Retrospective – Single centre – Nonrandomized	176	113 (45 LR)	63 (45 OR)	– Matching by cause of cirrhosis, CP score, tyoe surgical resection, tumor number, size and AFP. – All patients had confirmed F4 cirrhosis.	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this study was to compare morbidity, mortality and long-term patient survival between LR and OR for HCC in patients with histologically proven cirrhosis.

Limitations: Despite the fact that LR and OR groups were matched, the study is not randomized and thus some selection bias may exist related to the tumor accessibility that may play a role in the R0 outcome.

Conclusions: LR group displayed a shorter operative time (p=0.02), shorter hospital stay (p<0.0001) and lower morbidity rate at 90-day (p=0.01). A higher rate of R0 resection was observed in the LR group than in OR (p=0.03). the presence of postoperative ascites was more frequently observed in OR (p=0.01). There was no difference in overall survival and disease-free survival rate in both groups.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Kim H, Suh K-S, Lee K-W, Yi N-J, Hong G, Suh S-W, et al. **Long-term outcome of laparoscopic versus open liver resection for hepatocellular carcinoma: a case-controlled study with propensity score matching**.				2014	Surg Endosc	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Case control – Retrospective – Propensity score matching (1:1) – Single centre – Nonrandomized	1566 (205)	43 (29 after PSM)	162 (29 after PSM)	– PSM were generated with sex, age, ASA, BMI, underlying liver disease, preoperative laboratory, CP score, history of preoperative procedure for HCC, size and number tumor, location, range of resection.	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this study was to compare the preoperative and long-term oncologic outcomes of LR vs OR for HCC between well-matched patient groups.

Limitations: Only minor resection. The total number of patients was relatively small in both groups. Retrospective, non-randomized and observational study. The surgeons perhaps tended to select LR only in relatively simple and superficial lesión and easy case.

Conclusions: The hospital stay is significantly shorter than OR group and postoperative ascites occurred much less in the LR group. There were no differences of pathologic results including resection margin, and overall complications and major complications more than grade II of Clavien-Dindo grade. Recurrence tended to be earlier in the LR group but not a significant difference (p=0.120). There was no differences in overall survival time and overall disease-free survival time between the LR and OR groups. The present study showed that the outcome of LR for HCC was technically feasible and safe in selected patients. LR showed similar perioperative and long-term oncologic outcomes when compared with OR base don the casecontrolled study with PSM.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Kim S-J, Jung H-K, Lee DS, Yun SS, Kim HJ. **The comparison of oncologic and clinical outcomes of laparoscopic liver resection for hepatocellular carcinoma.**				2014	Annals of surgical treatment and research	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Case-control – Retrospective – Case-matched comparative analysis	146	70 (laparoscopic group)	76 (open group)	– Control were selected by PSM method and matched for sex, age, INR, albumin, AFP, AST, ALT, Blna, ICG, hepatitis, tumor location and size and type of resection.	• **++ High quality** • + Acceptable • - Low quality

This case-control study evaluate the operative outcome and oncologic outcome of laparoscopic liver resection for HCC and compare with open liver resction. Matching by PSM method.They did a subgroup analysis based on the type of treatment of first recurrence (distributions of treatment after recurrence were similar between two groups (p=0.360).

Limitations: No difference in hospital stay because they did a CT control at 7 day of postoperative time. All patients must be at least 7 days admitted to hospital.

Conclusion: Laparoscopic liver resection for HCC is feasible and safe in a large number of patients, and not inferior to open liver resection in regard to perative outcome. Oncologic outcome of laparoscopic liver resection for HCC is not inferior to open liver resection.

Guideline topic: HCC-comparative	
CQ	What is the role of LLR in cirrhotic patients?

Siniscalchi A, Ercolani G, Tarozzi G, Gamberini L, Cipolat L, Pinna AD, et al. **Laparoscopic versus Open Liver Resection: Differences in Intraoperative and Early Postoperative Outcome among Cirrhotic Patients with Hepatocellular Carcinoma-A Retrospective Observational Study**.				2014	HPB surgery: a world journal of hepatic, pancreatic and biliary surgery.	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control	– Case-control – Retrospective – Non-randomized – Comparative	194	23 (LR) (33 patients; 5 excluded for lack of data, 5 for conversion)	133 (OR) (166 patients; 28 were excluded for major hepatectomy)	– Matching for type of resection, median number of nodules, and median diameter of largest lesions. Preoperative liver and renal function tests. – They study the MELD score and renal function (before and after surgery).	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this study was to identify the differences in terms of perioperative complications and early outcome in cirrhotic patients undergoing minor hepatic resection for HCC with open or laparoscopic technique. In statistical analysisthey used a two linear model for repeated measures using the group membership as a factor between the subjects. The open group was worse Cr ($p<0.001$) and worse MELD.

Limitations: The control patients had larger (>5 cm), central, bilateral or connected with liver hilum, major hepatic veins or the IVC tumor. For this reason, the patients in control group were more complex. Patients in both groups underwent minor liver resection. There was not major liver resection in this study.There is an important difference in simple size between the two groups and its retrospective nature. Significant difference in the average age of the two groups (lower in the LR).

Conclusion: The patients in LR presented lower incidence of AKI (0% vs 6.8%) and postoperative liver faliure. Reduced necessity for transfusión of blood products. Lower values of MELD score after LR. Lower postoperative ascites (ns).

Mortality, morbility and postoperative hospital stay were lower. The advantages of laparoscopic liver resection compared to traditional technique are several, especially if laparoscopic approach is used in patients with higher MELD score and with a potencially increased risk of perioperative complications.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC? What is the role of LLR in cirrhotic patients?

Kanazawa A, Tsukamoto T, Shimizu S, Kodai S, Yamazoe S, Yamamoto S, et al. **Impact of laparoscopic liver resection for hepatocellular carcinoma with F4-liver cirrhosis.**				2013	Surg Endosc	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Case-control – Retrospective – Single centre – Non-randomized.	245 (56)	28 (LR)	28 (OR)	– Patients who underwent partial hepatectomy for HCC (3 cm or smaller in a dimater) in the surface area of the liver and had complete liver cirrhosis diagnosed histologically.	• ++ High quality • **+ Acceptable** • - Low quality

The purpose of this study was to compare the feasibility and safety of LR for HCC in cirrhotic patients with those of open liver resection in the same period.

Limitations: The inclusion criteria are very strict. Therefore this study is focused on patients with a precise characteristics. Reproducibility of it is difficult, and its application in the population is complicated. ONly for patients with liver cirrhosis and specific tumor characteristics. This is a retrospective study and with a small numbers of patients.

Conclusions: The intraoperative blood loss was lower lower in the LR than OR (p=0.0003). The incidence of the postoperative complications was significantly higher in the OR than in LR (p<0.001). The duration of the postoperative hospital stay was significantly shorter in the laparoscopy group than in OR (p<0.001). IN conclusión, even in cirrhotic patients, the laparoscopic liver resection decreased the incidences of intractable ascites and SSI, consequently shortened the length of the postoperative hospital stay.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC? What is the role of LLR in cirrhotic patients?

Cheung TT, Poon RTP, Yuen WK, Chok KSH, Jenkins CR, Chan SC, et al. **Long-term survival analysis of pure laparoscopic versus open hepatectomy for hepatocellular carcinoma in patients with cirrhosis: a single-center experience.**				2013	Annals of surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control	– Case control – Retrospective – Non-randomized – Matching 1:1 – Single centre.	600	32 (LR)	64 (OR)	– Matching in terms of cancer stage, tumor size, location of tumor and magnitude of resection. – The magnitude of surgery in both groups was comparable.	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this study was to analyze the survival outcome of laparoscopic liver resection versus open liver resection in patients with HCC

Limitations: Retrospective non-randomized study. Small number of patients. Inclusion criteria very strict therefore, the number of patients each group is small. The diagnosis of cirrhosis was after surgery.

Conclusions: The median hospital stay was shorter in LR ($p<0.0001$). The LR group showed low median blood loss ($p=0.001$). There were no differences in overall survival and disease-free survival rate at 1-, 3- and 5-years in both groups (this study is the first report to comment on the long-term survival of patients with HCC in reference to the stage of disease). Laparoscopic liver resection for HCC is associated with less blood loss, shorter hospital stay and fewer postoperative complications in selected patients with no compromiso in survival.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Kobayashi S, Nagano H, Marubashi S, Kawamoto K, Wada H, Eguchi H, et al. **Hepatectomy based on the tumor hemodynamics for hepatocellular carcinoma: a comparison among the hybrid and pure laparoscopic procedures and open surgery**				2013	Surg Endosc	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Cohorts retrospective	– Cohort study – Retrospective analysis – Colleted prospective – Non randomized – Single centre	129	Pure=24 Hybrid=29 HALS=3	27 (OR)	– Solitary HCC tumors measuring less than 3 cm located in segment 2, 3, 4, 5, or 6, with no macroscopic evidence of vessel invasion, in patients who had not received any preoperative treatments.	• ++ High quality • **+ Acceptable** • - Low quality

This study was designed to evaluate the surgical parameters and treatment outcomes of tumor hemodynamics-based pure laparoscopic (PURE) and laparoscopy-assisted (HYBRID) hepatectomy for small HCC compared with those of open hepatectomy.

Limitations: In the survival analyses they excluded patients with HCC more than 3 cm in diameter. Nonrandomized. Retrospective.

Conclusions: Pure and Hybrid were not inferior to OPEN, PURE was associated with a lower resected liver weight, lesser blood loss and smaller skin incisión than HYBRID and OPEN. The duration of hospitalization was shorter for PURE and HYBRID than for OPEN. The operation time for HYBRID was longer than for PURE and OPEN. There were no statistically significant differences in the overall survival or disease free survival between LAP and OPEN. From these evaluations of 50 consecutive cases, we concluded that the surgical and treatment outcomes of our hemodynamics-based laparoscopic hepatectomies were not inferior to those of open hepatectomy performed at our institution.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Ai J-H, Li J-W, Chen J, Bie P, Wang S-G, Zheng S-G. **Feasibility and safety of laparoscopic liver resection for hepatocellular carcinoma with a tumor size of 5-10 cm.**				2013	PLos ONE	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Retrospective – Simple Centre – Case-control – Non-randomized. – Observational	275	97 LR	178 (OR)	– The 178 patients in the OR were considered potential candidates for LR but underwent OR as a control group, with permission from the patients and theis dependents. The preoperative HCC characteristics were similar between LR and OR.	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this study was to explore the safety and feasibility of laparoscopic liver resection for the treatment of HCC with a tumor size of 5-10 cm. There were no significant differences in mean operative time (p=0.469), mean stimated intraoperative blood loss (p=0.913), or blood transfusión rate (p=0.480) between lap and open group. There was a lower rate of postoperative complications in LR than OR. Postoperative hospital stay was shorter in the LR group (p=0.028). Median overall follow-up time was 25 months in the LR and 20 months in OR. There were no significant differences in the 1-year and 3-years overall survival and disease-free survival.

Limitations: Small sample. Retrospective study. Short follow up to study oncological outcome as recurrence. Only the time period were matched between the two groups. The most complex cases, as patients with previous surgery were excluded fron LR group.

Conclusions: LR for HCC with a tumor size of 5-10 cm is safe and feasible, even in appropiately selected patients with liver cirrhosis.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Hu B-S, Chen K, Tan HM, Ding X-M, Tan JW. **Comparison of laparoscopic vs open liver lobectomy (segmentectomy) for hepatocellular carcinoma.**				2011	World Journal of Gastroenterology	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Cohort study	– Cohort study – Retrospective – Non-randomized – Single centre	60	30 LR	30 (OR)	– The patients in the OR group were retrospectively selected by the same criteria than LR group. – No differences in any of the preoperative backgroung variables between the two groups (including tumor size).	• ++ High quality • + Acceptable • **- Low quality**

The aim of this study was to investigate the effects of laparoscopic hepatectomy for the treatment of HCC.

Limitations: Very small sample. They only did one control per case. The recurrence and survival rate are low (although there were no significant differences) and do not show that % of patients completed follow up at 5 years.

Conclusions: Outcomes postoperative, patients in the LR group started walking and eating significantly earlier, recovered was more rapidly and shorter hospitalization. No difference statistical significance in complication rate.There were no differences in the survival rate or disease-free survival rate. Laparoscopic liver resection is a safe and feasible treatment option for HCC, even in cirrhotic liver, however further evaluation is required.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC? What is the role of LLR in cirrhotic patients?

Truant S, Bouras AF, Hebbar M, Boleslawski E, Fromont G, Dharancy S, et al. **Laparoscopic resection vs. open liver resection for peripheral hepatocellular carcinoma in patients with chronic liver disease: a case-matched study.**				2011	Surgical Endoscopy	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Retrospective – Case-control – Matched-pair analysis	122	36 LR	53 (OR)	– The two groups were similar in term of tumor number and size and number of resected segments. – Intention-to-treat basis	• ++ High quality • **+ Acceptable** • - Low quality

This study dertermined the impact of laparoscopic resection on postoperative and long-term outcomes in a large series of cirrhotic patients with HCC compared with open resection. This is one of the largest case-matched studies of LR vs OR.

Limitations: Small number of patients. Tumor location according to liver segment was not considered in the matching criteria. Do not explain the inclusión cirteria for open group.

Conclusions: The two groups were similar in terms of mean operating time, vascular clamping, blood transfusions with similar blood loss. 4 died in OR (0% vs 7.5% p=0.3). Similar overall morbility rate in both groups (25% vs35.8%; p=0.3). There was a non significant (p=0.09) trend toward a higher rate of severe complications in the OR than in LR group. The mean duration of hospitalization was significantly shorter in LR (p=0.003). Overall 5 year survival tended to be higher in the LR (p=0.073) and five year disease-free survival was similar in two groups (p=0.8). The laparoscopic approach was particularly beneficial in cases of portal hypertension complicated by postoperative ascites and cirrhotic liver.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Lee KF, Chong CN, Wong J, Cheung YS, Wong J, Lai P. **Long-term results of laparoscopic hepatectomy versus open hepatectomy for hepatocellular carcinoma: a case-matched analysis**				2011	World Journal of Surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Case- control – Retrospective – Non-randomized – Single centre	233	33 LR	50 (OR)	– Matching to magnitude of operation, size tumor, site of tumor, and the absence of concominant local ablation or major procedure. – Intention-to-treat basis	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this study was evaluate the long-term results of LH compared with a cohort of case-matched open hepatectomy.

Limitations: There were more patients in LR group underwent left lateral sectionectomy (improve the resection margin). There were more cirrhotic patients in the LH group. They did a subgroup analysis in order to get the difference between LLS and cirrhotic patients but the findings may not be strong because the sample is very small.

Conclusions:Compared with OH, LH for HCC has similar long-term outcomes, but it has short-term advantages of less operative complications and shorter hospital stay. The resection margin was significantly wider in LR than OR (p=0.016). There was no mortality in both groups and less complications in LR group. No difference in blood loss and blood transfusión rate. The operative time was significantly longer in LH but hospital stay was shorter than in OR group. There was no significant difference between the two groups in overall and disease-free survival at 5 years postoperatively.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Kim HH, Park EK, Seoung JS, Hur YH, Koh YS, Kim JC, et al. **Liver resection for hepatocellular carcinoma: case-matched analysis of laparoscopic versus open resection**				2011	Journal of Korean Surgical Society	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control matched	– Retrospective – Case-control – Non-randomized – Single centre	102	26 LR	29 OR (from 73 patients)	– Matched in terms of demographic data, tumor size, degree of liver cirrhosis, ASA score, type of resection and tumor location	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this study was to analyze the outcomes of laparoscopic liver resection compared with open liver resection for HCC using a case-matched analysis. No difference was found between the two groups for the type of resection (p=0.467).

Limitations: Small number of cases. Study non-randomized. There are several bias as selection bias related to the choice of approach based merely on tumor characteristics.

Conclusions: This study confirmed the feasibility, safety, and benefits of laparoscopic liver resection for selected patients, including HCCs located in segments 7 and 8 and major hepatectomies. Laparoscopic liver resection for HCC lead good surgical results with a shorter postoperative hospital stay, shorter operating time, less intraoperative bleeding, and similiar outcomes in terms of disease-free survival when compared with open surgery.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Nguyen KT, Marsh JW, Tsung A, Steel JJL, Gamblin TC, Geller DA. **Comparative benefits of laparoscopic vs open hepatic resection: a critical appraisal.**				2011	Arch Surg	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control matched	– Literature review of 2473 patients (31 publications). – Case control study at single tertiary centre.	1294	314 LR (24.3%) (45.4% malignant) 17 for HCC (10 hand-assited and 7 pure laparoscopic)	20 OR for HCC	– There were no significant differences in sex, age, percentage of patients with cirrhosis, type of resection, concurrent resection, or concurrent procedure for HCC group.	• ++ High quality • **+ Acceptable** • - Low quality

Limitations: Is a retrospective analysis. There is some variation as to the selection criteria among surgeons (selection bias). Small number of patients with HCC.

Conclusions: The LR for HCC had a significantly smaller BMI compared with OR. There were no statistical differences between the tumor size and percentage of negative margins between LR or OR. OR was associated with significantly closer negative margins than the LR (p=0.04). There were no statistically significant differences in operative time, blood loss, or transfusión rate. The complication rates were nor significantly different. The length os stay was significantly shorter for patients who underwent LR (p=0.002). Disease free survival was significantly better for the LR compared with OR and no difference in terms of overall survival. For patients with HCC, the operating room costs for the laparoscopic liver resection were not significantly higher than the operating room costs for open liver resection cases ($1.14 vs $1.03; P=.68). In addition, the total hospital costs were not significantly different between the 2 groups ($1.85 vs $2.00; P=.39).

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Ker CG, Chen JS, Kuo KK, Chuang SC, Wang SJ, Chang WC, et al. **Liver Surgery for Hepatocellular Carcinoma: Laparoscopic versus Open Approach**				2011	Int J Hepatol	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control study	– Retrospective – Case-control – Non-randomized – Single centre	324	116 LR	208 OR	– No difference in both groups related to overall survival and disease-free survival rate.	• ++ High quality • **+ Acceptable** • - Low quality

This study tried to compare the benefit of laparoscopic versus open operative procedures doing a case-control retrospective single centre study.

Limitations: There were important bias in this study. The tumor size was bigger in OG, the patients in OR underwent more complex resection (>2 segments) with statistically significance difference.

Conclusions: Postoperative complications were more frequent in OR group (p=0.001). The developed of transient ascites was more frequent in OR group (p=0.002).Mean Hospital stay was shorter in LR group (p=0.001). After a man follow-up of 94 months there were no significant differences in relation to overall survival rate and disease-free survival rate at 1-, 3-, 5- year. Laparoscopic hepatectomy is beneficial for patient life quality as a minimally invasive procedure, is more feasible and with a low morbility and mortality rate comparable to open procedures.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Alemi F, Kwon E, Freise C, Kang S-M, Hirose R, Stewart L, et al. **Hepatic surgery at a VA tertiary medical center: lessons learned.**				2010	The American Journal of Surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Cohorts retrospective study	– Retrospective cohorts study – Single centre	126 patients	28 LR (with RFA 46; only lap 33)	25 OR	– Review the spectrum of liver disease treated by surgery – Focus the analysis in patients with chronic hepatitis C virus-related HCC and liver cirrhosis. – Cohorts retrospective study	• ++ High quality • **+ Acceptable** • - Low quality

This study hypothesize that appropriate fellowship training combined with a supportive hospital environment can translate into low operative morbility and mortality rates even at low-volume medical centers.

Limitations: Retrospective character of the study. Small sample size. Patients selected to undergo the laparoscopic resections were treated more often by either wedge resection or segmental resection compared with patients treated by the open technique. Selection bias.

Conclusions: Significantly lower intraoperative blood loss and need for transfusión in lap group. No significant difference in hospital stay between the two groups. Comparable complication rates, although the lap group have less severe wound complication and leakage of ascites. Appropriate training in HPB surgery can translate into aceptable perioperative outcomes that rival those obtained at high-volume training academic and nonacademic medical centers.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Yoon Y-S, Han H-S, Cho JY, Ahn KS. **Total laparoscopic liver resection for hepatocellular carcinoma located in all segments of the liver**				2010	Surgical Endoscopy	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Case control – Retrospective – Comparative – Nonrandomized – Single centre	177 patients	74 LR HCC 69 definitive HCC LR PS 25	AL 44	– LLR was applied as a totally laparoscopic procedure regardless of tumor location unless the tumor was larger than 5 cm, had invaded or was close to the main portal pedicle or major hepatic veins, or was located in the suprahepatic junction adjacent to the major hepatic veins.	• ++ High quality • **+ Acceptable** • - Low quality

This study evaluated clinical and oncologic outcomes after LLR for HCC located in all segments, including lesions located in the posterosuperior (PS) segments.

Limitations: Anatomical resection was perfomred more frequently in group PS than in group AL. Small number of patients. And nonrandomized study

Conclusions: There was a male predominance in group PS (p = 0.021), and there were more patients with thrombocytopenia less than 100 9 103 /mm3 in group AL (p = 0.001). Otherwise, there were no differences between the two groups in clinicopathologic characteristics. Nonanatomical liver resection was a more common operative procedure in group AL, whereas anatomical liver resection including right posterior sectionectomy and right hemihepatectomy was a more common operative procedure in group PS (p\ 0.001). COnversion rate was 7.2%. Operative time was longer in PS group (p=0.001), blood loss tended to be greater in PS group (p=0.068). The mean postoperative hospital stay was 9.7 days, longer for PS group (p=0-039). There were no statistically significant difference in survival and disease free survival rate in both groups. it was demonstrated that patients with HCCs in posterosuperior segments have a similar outcome compared with that of patients with HCCs in anterolateral segments.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Tranchart H, Di Giuro G, Lainas P, Roudie J, Agostini H, Franco D, et al. **Laparoscopic resection for hepatocellular carcinoma: a matched-pair comparative study.**				2010	Surg Endosc	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control study	– Retrospective – Case control (pair-matched)	156	42 LR (27%)	42 OR	– Matched for sex, age, ASA, Severity of liver disease, tumor siza, and type of resection. – Intention-to-treat basis. – The two groups did not differ significantly in terms of tumor characteristics, namely, tumor size, surgical margin, the presence of vascular invasion, a well-formed capsule and satellite nodules.	• ++ High quality • **+ Acceptable** • - Low quality

This study describes the results of a pair matched comparative study between OR and LR for HCC.

Limitations: The patients underwent laparoscopic approach presented smaller tumor, located in the inferior or anterior segments of the liver and distant from the portal pedicle or hepatic veins. Small number of patients and retrospective study. Only selected one control per each case.

Conclusions: LR of HCC for Significantly less bleeding was observed in LR ($p<0.0001$). Postoperative ascites was less frequent after LR ($p=0.03$). Severity of complications was similar in the two groups. The main hospital stay after surgery was shorter for the patients who underwent LR ($p<0.0001$). No difference in survival and disease-free survival rate in both groups at 1,3 and 5 year of follow-up.

selected patients gave a better postoperative outcome without oncologic consequences.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Aldrighetti L, Guzzetti E, Pulitanò C, Cipriani F, Catena M, Paganelli M, et al. **Casematched analysis of totally laparoscopic versus open liver resection for HCC: short and middle term results.**				2010	J Surg Oncol	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control study	– Retrospective – Case-control – Single centre – Prospectively collected database	56	16 LR	16 OR	– Matched in terms of type of resection, tumor size and severity of cirrhosis. – The cases and controls are not from the same period of time.	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this study was to evaluate surgical results and mid-term survival of minor hepatic resection performed for HCC.

Limitations: The controls and cases patients are not from the same period of time (the OR were older than LR). All patients in LR underwent minor resection. Short follow-up of patients.

Conclusions: Mean operative time was shorter in LR (p=0.044). Less intraoperative blood loss (p=0.008). Postoperative complications in both groups are not statistically difference. Mean hospital stay was shorter in LR (p=0.039). Both groups showed similar outcomes in terms of overall and disease-free survival. Laparoscopic approach does not impair the oncological outcomes of surgery for HCC.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Zhen ZJ, Lau WY, Wang FJ, Lai ECH. **Laparoscopic liver resection for hepatocellular carcinoma in the left liver: Pringle maneuver versus tourniquet method.**				2010	World Journal of Surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control	– Retrospective – Nonrandomized – Comparative – Single centre	29	16 Pringle maneuver (A)	13 tourniquet method (B)	– Selected patients with normal or mildly cirrhotic liver, tumor size B 8 cm, and tumor located at Couinaud segments II, III, or IV for laparoscopic resection. – Both group were matched in the demographic data, tumor size, severity of cirrhosis and surgical procedures.	• ++ High quality • **+ Acceptable** • - Low quality

The objective of this nonrandomized comparative study was to compare the efficacy of the tourniquet method with the Pringle maneuver in laparoscopic liver resection for HCC in the left liver.

Limitations: Very small sample. This study because of its small sample can not draw conclusions that easily extrapolated to the target population. Technique very dependent on the surgeon performed it would be desirable way of multicentric study. Non randomized.

Conclusions: There were no differences in the operation time, operative blood loss, and perioperative blood transfusión between the two groups. The postoperative hospital stay for group B was significantly shorter than group A. Group A had significantly higher ALT levels on the first postoperative day compared with group B. The liver function in group B recovered significantly faster than group A (P\ 0.01). The torniquet method gave a wider safety margin for patients with chronic liver disease with a compromised hepatic reserve by causing less ischemia reperfusión injury to the remnant liver.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Endo Y, Ohta M, Sasaki A, Kai S, Eguchi H, Iwaki K, et al. **A comparative study of the long-term outcomes after laparoscopy-assisted and open left lateral hepatectomy for hepatocellular carcinoma.**				2009	Surg Laparosc Endosc Percutan Tech.	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Retrospective cohorts matched	– Cohorts – Retrospective – Non-randomized – Matched (1:1)	21 LLS (278 in total)	10 LAR (laparoscopy-assisted)	11 OR (open conventional)	– Patients themselves chose which procedures they preferred.	• ++ High quality • **+ Acceptable** • - Low quality

The aims for this study were to assess our results of laparoscopy-assisted left lateral hepatectomy for HCC and to compared them with those of open conventional procedures.

Limited: Only patients with tumor less than 5 cm. One inclusión criteria was no earlier history of operation in the upper abdomen. Each group comes from different period of time. The patients who underwent LAR were older than OR ($p<0.01$).

Conclusions: There were no significant differences in the mean operation time, blood loss, resected liver weight and resected margin between two groups. There were no significant differences in morbidities between the groups. Postoperative hospital stay were statistically better in laparoscopy-assisted group than those in open group. There were no significant differences in the survival and disease-free survival rate between the 2 groups. Laparoscopy-assisted hepatectomy may be a useful alternative for the treatment of HCC less than 5 cm in diameter.

Guideline topic: HCC-comparative	
CQ	What is the role of LLR in cirrhotic patients?

Belli G, Limongelli P, Fantini C, D'Agostino A, Cioffi L, Belli A, et al. **Laparoscopic and open treatment of hepatocellular carcinoma in patients with cirrhosis**				2009	British Journal of Surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Retrospective cohorts	– Cohorts – Retrospective – Single centre – Non-randomized	179	54 LR	125 OR	– Surgical experience in LR were assessed by comparison of two time periods: before and after November 2004. – Did a subgroup analysis of patients stratified respect tumor characteristics to show the influence on cancer outcomes	• **++ High quality** • + Acceptable • - Low quality

Retrospective analysis of 179 liver resections performed for HCC in cirrhotic liver.

Limitations: Patients who underwent by laparoscopic approach were smaller size tumor and liver resection was less extensive than in the open resection. Those patients with complicated cirrhosis or whose ASA grade exceded III were excluded from resection. The more complex tumor (big, next to vessels, postero-superior segments were excluded from laparoscopic group). Only three major hepatectomy were performed in LR ($p<0.001$)

Conclusions: Pringle manoeuvre was used in one patient in the LR group and 26 in OR group ($p<0.001$). Patients underwent LR had a higher proportion wide resection margin ($p<0.001$). There were no significant differences in overall and disease-free survival rates between LR and OR groups.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Sarpel U, Hefti MM, Wisnievsky JP, Roayaie S, Schwartz ME, Labow DM. **Outcome for patients treated with laparoscopic versus open resection of hepatocellular carcinoma: casematched analysis.**				2009	Annals of surgical oncology	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control study	– Case-control – Retrospective – Non-randomized – Single centre	76	20 LR	56 OR	– Matching by cirrhosis and tumor size – Multivariate models were adjusted for age, sex, presence of cirrhosis and tumor size.	• **++ High quality** • + Acceptable • - Low quality

The aim of this project was to perform a case-matched analysis of patients undergoing laparoscopic versus open liver surgery for HCC, with specific regard to margin status and survival.

Limitations: Small number of patients. The study was done in a huge period time. For this reason in several results, for example the duration of the surgery, the learning curve could influence.

Conclusions: Multivariate analyses showed that patients undergoing LR have similar rates of intraoperative transfusión, and positive margins compared with open group. The adjusted odds of length of stay ≥6 days was significantly lower in patients treated with LR (OR=0.07, 95% CI=0.02-0.27). Also showed that liver cirrhosis significantly increased the risk for transfusión (OR=8.01, 95% CI=1.29-49.61). Neither margin status, nor recurrence, nor survival was significantly different between the two cohorts. Laparoscopic resection for malignancy is safe, with a similar operative time as open hepatectomy. If tumor location is amenable, laparoscopic resection for HCC is a reasonable alternative to open resection with the added benefits of improved cosmesis and sooner discharge home.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Lai ECH, Tang CN, Ha JPY, Li MKW. **Laparoscopic liver resection for hepatocellular carcinoma: ten-year experience in a single center.**				2009	Arch Surg	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Nonrandomized comparative study	– Retrospective – Non-randomized – Case-control – Single centre	58	25 LR	33 OR	– Matching in terms of demographic data, tumor size, severity cirrhosis and surgical procedure. – Inclusion criteria: Normal livers or CP A, tumor size of 5 cm or less, tumor location at the anteroinferolateral segments. Solitary exophytic tumors larger than 5 cm that were accessible by LR.	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this Comparative study was to study the feasibility, safety and mid term results of laparoscopic liver resection of HCC.

Limitations: In this series most of the procedures (84%) used the hand-assisted laparoscopic approach. Non-randomized. Small number of patients with HCC.

Conclusions: No differences in operation time, postoperative complication rate, and hospital mortality rate were found between the 2 groups. The postoperative hospital stay for LR was significantly shorter than for OR (p=0.008). No differences between procedures with regard to overall (p=0.23) and disease-free survival rate (p=0.14) at 3-year. Laparoscopic hepatectomy for HCC is feasible and safe in selected patients. Midterm survival is also

favorable. The laparoscopic approach has the benefit of a shorter hospital stay. However, the procedure should be

performed by a surgical team expert in hepatobiliary and laparoscopic surgery in properly selected patients.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Cai XJ, Yang J, Yu H, Liang X, Wang YF, Zhu ZY, et al. **Clinical study of laparoscopic versus open hepatectomy for malignant liver tumors.**				2008	Surg Endosc	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case-control study	– Pair matched – Retrospective – Single centre – Nonrandomized	62	31 LR (24 HCC specimen)	31 OR (26 HCC specimen)	– The groups were matched for age, sex, the size and location of the tumor and the presence or absence of cirrhosis. – Subgroups analyses in term of period of time	• ++ High quality • **+ Acceptable** • - Low quality

The aim of this study was to evaluate the intraoperative hazards, recovery and survival outcomes of theses procedures for liver cancer.

Limitations: Retrospective study, non-randomized. The patients of this study have tumors of different etiology: HCC, Metastasis, cholangiocarcinoma and for this reason the curves of survival and recurrence should not be construed in the same way.

Conclusions: The length of hospital stay was 7.5(5-15) days, which was significantly shorter than those in OR ($p<0.01$). By log-rank test, the two survival curves (overall survival and disease-free survival) were not significantly different.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Chen H-Y, Juan C-C, Ker C-G. **Laparoscopic liver surgery for patients with hepatocellular carcinoma.**				2005	Annals of Surgical Oncology	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control – Comparative	– Retrospective – Case control – Single centre – Non randomized	116 LR	97 VR less than 2 segments (Group I)	19 VR more than two segments (group II)	– The criteria for liver resection were HCC, with pathological diagnosis before operation, whichwas found to be resectable after imaging and clinicalstudies. The indications for a laparoscopic procedure were tumor located in the peripheral part of left liver or the anterior sector of right liver, and the size less than 5 cm in diameter	• ++ High quality • + Acceptable • **- Low quality**

This is a retrospective study of patients with HCC treated by liver resection with a totally laparoscopic approach.

Limitations: This is a poor study with a Little clinic transcendence. The numbers of patients is very small. It is no clear if the approach of the patients is pure laparoscopic in all of them or if they used hand-assisted. Non randomized.

Conclusions: Conversion rate was 5.2%. The average length hospital stay was 6 days. Blood transfusion was necessary in five patients (5.2%) in group I and three patients (15.8%) in group II (p = 0.122). After a mean follow up duration of 94 months, the 1-year, 3-year, and 5-year survival rates were 85.4% , 66.4% , and 59.4% in group I, and 94.7% , 74.2% , and 61.7% for group II, respectively. There was no significant difference in survival rates between the two groups (p = 0.1237).Laparoscopic liver resection is feasible in HCC of the tumor is singular, smaller than 5 cm and located in the left lateral segments or anterior or inferior sector of the right liver. laparoscopic hepatectomy could avoid some of the disadvantages of open hepatectomy and is beneficial for patient quality of life, as a minimally invasive procedure.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Kamiyama T, Kurauchi N, Nakagawa T, Nakanishi K, Kamachi H, Matsushita M, et al. **Laparoscopic hepatectomy with the hook blade of ultrasonic coagulating shears and bipolar cautery with a saline irrigation system.**				2005	J Hepatobiliary Pancreat Surg	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control	– Retrospective – Single centre – Nonrandomized	18	8 LR	10 LLS open	– The characteristics of patients who had the laparoscopic left lateral segmentectomy were not significantly different from those of the patients who had had a left lateral segmentectomy with laparotomy	• ++ High quality • + Acceptable • **- Low quality**

They report their experience with seven anatomical and 1 nonanatomical laparoscopic hepatectomies, performed with a hook blade of ultrasonic coagulating shears, and bipolar cautery with a saline irrigation system, with minilaparotomy.

Limitations: In all patients they performed cholecystectomy to prevent cholecystitis (after probably TACE in the future) –this do the operative time longer than other studies- Small number of patients. Non randomized. Nowadays this is a old study because the gold estándar treatment for the LLS in the pure laparoscopic approach (case control, randomized and metaanalyses).

Conclusions: The overall mean postoperative hospital stay was 9.88 (median 8 days). The time of surgery and the hospital stay were significantly shorter than in open group. The mean amount of blood loss was less in LR group. In this study they dissected the liver parenchyma with the hook blade of ultrasonic coagulating shears and performed bipolar cautery with a saline irrigation system, without inflow occlusion in combination with a minilaparotomy.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Kaneko H, Takagi S, Otsuka Y, Tsuchiya M, Tamura A, Katagiri T, et al. **Laparoscopic liver resection of hepatocellular carcinoma.**				2005	The American Journal of Surgery	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Case-control – Matching 1:1 – Retrospective – Single centre – Non-randomized	144	30 HCC LR	28 OR	– The groups have the same inclusion criterias – Subgroups analyses in term of period of time (shorter operative time in recent time)	• ++ High quality • + **Acceptable** • - Low quality

To evaluate less invasive surgery, they used the Estimation of Physiologic Ability and Surgical Stress (E-PASS) scoring system, which predicts postoperative morbidity and mortality by quantifying the patient's reserve and surgical stress.

Limitations: All HCCs were localized in the left lobe or lower segment (except 1 case). Retrospective and nonrandomized study.

Conclusions: The patients started walking and eating significantly earlier in LR group group and shorter hospitalizations. According to the E-PASS score there was no difference in preoperative risk. Bur a significant difference was seen in the surgical stress and comprehensive risk scores between the OR and LR groups. Survival rate and disease-free survival rate were no significant differences between both group at 5 years. The laparoscopic approach in selected patients with HCC should be considered the treatment of choice.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Laurent A, Cherqui D, Lesurtel M, Brunetti F, Tayar C, Fagniez PL. **Laparoscopic liver resection for subcapsular hepatocellular carcinoma complicating chronic liver disease.**				2003	Arch Surg	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Case control – Retrospective – Single centre – Non-randomized	27	13 LR	14 OR	– Inclusion criteria: Tumors were 5 cm or smaller, subcapsular, and located in anterolateral segments (II-VI) – Matching with identical liver disease, tumor size, location and type of hepatectomy	• ++ High quality • + **Acceptable** • - Low quality

A case-comparison study. The aim of study is show laparoscopic liver resection for subcapsullar HCC in patients with chronic liver disease is associated with lower morbility than open resections.

Limitations: Only psubcapsular tumor, small size and no major hepatectomy included. This study is limited by the relatively small number of patients. Retrospective nature. The results in relation to surgery time is due to learning curve effect.

Conclusions: Operative duration (p=0.006) and cumulative clamping time (p=0.006) were significntly longer in LR group. There were no differences in mortality (p=0.2), morbility (ns) and hospital stay (0.83) in both groups. Overall 3-year survival was significantly higher in LR group (89% vs 55% p=0.04). Recurrence-free survival was similar in both groups.

LR os subcapsular HCC in cirrhotic patients is safe but requires specific training and it may have a higher burden on operating room ressources.

Guideline topic: HCC-comparative	
CQ	Are LLR indicated for the management of HCC?

Shimada M, Hashizume M, Maehara S, Tsujita E, Rikimaru T, Yamashita Y, et al. **Laparoscopic hepatectomy for hepatocellular carcinoma.**				2001	Surg Endosc	Laparoscopic surgery in HCC
Study type	**Specifications on study design**	**Study Group**		**Control Group**	**Notes**	**Study quality**
		Patients	**Cases**			
– Case control study	– Case control – Retrospective – Single centre – Non-randomized	285	17 LR	38 OR	– Inclusion criteria: First hepatectomy, Tumors were 5 cm or smaller, Solitary tumor, and located in anterolateral segments (II-VI) or LLS. – Matching with inclusion criteria and the time period.	• ++ High quality • + **Acceptable** • - Low quality

This case-control study presented their long experiences with laparoscopic hepatectomy for HCC. Also discussed the importance of this procedure from the viewpoints of both short- and long-term outcomes.

Limitations: The % of cases and controls extracted from the population is small. So the statistical power of this study is low. It does not explain exactly why perform splenectomy in some patients (18%). The operative time was longer maybe for this reason. Only included patients with tumor localized in left lateral segments or anterior (the more complex resection were excluded).

Conclusions: The postoperative hospital stay of LR was significantly shorter than OR (<0.001). Operative time tended to be longer and blood loss tended to be smaller in LR than in the OR group. The found no difference in the patients survival rate and disease-free survival rate between the two groups.

APPENDIX 5

Considered Judgement Form
Part B – Evidence to recommendations
Proforma

CQ *: Are LLR indicated for the management of HCC?
a. Short term outcomes
b. Oncologic and Long term outcomes

B.1 *Balancing benefits and harms (see SIGN 50, section 6.2.2, 6.2.3)*
Comment here on the potential clinical impact of the intervention/action – eg. magnitude of effect; balance of risk and benefit.

B.1.a *What benefit will the proposed intervention/action have?*
Describe the benefits. Highlight specific outcomes if appropriate.

Potential benefits from the laparoscopic approach of HCC patients may come from:
- Improved outcomes for HCC patients with reduced complications
- Short hospital stay, less blood loss, less transfusion rate, fewer complications rate.
- Better esthetical impact due to reduced surgical incision.
- Against those who previously thought, due to laparoscopic approach a better visualization for liver transection and better control of bleeding is achieved.

B.1.b *What harm might the proposed intervention/action do?*
Describe the benefits. Highlight specific outcomes if appropriate.

There are no specific harms derived from the laparoscopic approach in HCC patients.

B.2 *Impact on patients (see SIGN 50, section 6.2.4, 6.2.5)*
Is the intervention/action acceptable to patients and carers compared to comparison?
Consider benefits vs harms, quality of life, other patient preferences (refer to patient issues search if appropriate).
Are there any common comorbidities that could have an impact on the efficacy of the intervention?

The laparoscopic approach offers benefits over patients who are offered. In comparative studies, the patients in the open group often come from prior periods in which laparoscopic approach was not performed in all centres. This is the selection bias which exist in these studies. Because patients in the open group use to be patients with bigger tumour size, closer to main vessels or with previous surgery that are expected to could not be performed by laparoscopic approach.

B.3 *Feasibility (see SIGN 50, section 6.2.6)*
Is the intervention/action implementable in the European context? Consider existing cost effectiveness, financial, human and other resource implications.

The intervention is totally feasible in the European context. Cost effectiveness may not be significative, considering the reduced postoperative complications and hospital stay.

B.4 *Recommendation (see SIGN 50, section 6.3)*

B.4.a What recommendation(s) does the guideline development group agree are appropriate based on this evidence?

Strong recommendation: Laparoscopic approach in HCC patients is not inferior in terms of operative mortality, margin negativity, overall survival and disease free survival. (major and minor resection)
Strong recommendation: Laparoscopic approach is superior than open approach in term of hospital stay, transfusion rate, operative time, blood loss and postoperative complications.
Conditional recommendation: Regarding complex resection as posterosuperior segment and major resection or lesion very close to hepatic pedicle should be considered with caution, there are insufficient data about that and need more studies.
Recommendation for research: Further research should be undertaken in the form of prospective randomized control trials to substantiate our findings even further.

B.4.b *"Strong" recommendation should be made where there is confidence that, for the vast majority of people, the intervention/action will do more good than harm (or more harm than good). The recommendation should be clearly directive and include 'should/ should not' in the wording.*
"Conditional" recommendations should be made where the intervention/action will do more good than harm (or more harm than good) for most patients, but may include caveats eg on the quality or size of the evidence base, or patient preferences. Conditional recommendations should include 'should be considered/ should not be considered' in the wording.

STRONG/CONDITIONAL

Strong recommendations for the use of laparoscopic approach for HCC patients in minor and major resections by specialized team is justified due to the number of comparative series and existing evidence.
There is insufficient evidence for complex resections as lesions in posterosuperior segments or very close to the hepatic pedicle, this decisions depends in strong way of the team experience. That is why conditional evidence is the current status.

5. *Recommendations for research* *List any aspects of the question that have not been answered and should therefore be highlighted as an area in need of further research.*
The main problem of selection bias should be considered for research: – To perform multicentre and randomized studies where will be possible to avoid the heterogeneity of the sample on each group. At the moment it has been tried to avoid instead of matching method and propensity score matching but it necessary to get randomized studies in the close future.

APPENDIX 6

Considered Judgement Form
Part B – Evidence to recommendations
Proforma

CQ *: What is the role of LLR in cirrhotic patients?

a. Short term outcomes
b. Oncologic outcomes
c. Special advantages / difficulties for cirrhotic patients
d. Technical aspects for liver resections in cirrhotics

B.1 *Balancing benefits and harms (see SIGN 50, section 6.2.2, 6.2.3)*
Comment here on the potential clinical impact of the intervention/action – eg. magnitude of effect; balance of risk and benefit.

B.1.a *What benefit will the proposed intervention/action have?*
Describe the benefits. Highlight specific outcomes if appropriate.

Potential benefits from the minimally invasive approach of cirrhotic HCC patients may come from:

- Improved outcomes for HCC cirrhotic patients with reduced complications
- Improved short term outcomes (less transfusion rate, less risk of bleeding, short hospital stay, low risk of liver failure)
- Better esthetical impact due to reduced surgical incision.
- Better control of bleeding due to improved laparoscopic visualization thanks to the image magnification during resection.

B.1.b *What harm might the proposed intervention/action do?*
Describe the benefits. Highlight specific outcomes if appropriate.

There are no specific harms derived from the laparoscopic approach.

B.2 *Impact on patients (see SIGN 50, section 6.2.4, 6.2.5)*
Is the intervention/action acceptable to patients and carers compared to comparison?
Consider benefits vs harms, quality of life, other patient preferences (refer to patient issues search if appropriate).
Are there any common comorbidities that could have an impact on the efficacy of the intervention?

The laparoscopic approach offers benefits over patients who are offered. Laparoscopic resection of HCC in patients with cirrhosis is safe and may provide improved outcomes when compared to the open technique.

B.3 Feasibility (*see SIGN 50, section 6.2.6*)
Is the intervention/action implementable in the European context? Consider existing cost effectiveness, financial, human and other resource implications.

The intervention is totally feasible in the European context. Cost effectiveness may not be significative, considering the reduced postoperative complications and hospital stay.

B.4 Recommendation (see SIGN 50, section 6.3)

B.4.a *What recommendation(s) does the guideline development group agree are appropriate based on this evidence?*

Strong recommendation: laparoscopic resection for Cirrhotic HCC patients is safe.
Strong recommendation: laparoscopic resection for cirrhotic HCC patient provide a better short outcomes as short hospital stay, less blood loss, less transfusion rate and low risk of complications (pleural effusion, ascites, pain…)
Strong recommendation: There are no differences in relation to oncological outcomes and long term between the two approaches.
Strong recommendation: Cirrhotic HCC patients underwent laparoscopic approach could be benefit from this approach in case of need transplant for recurrence. This approach reduces transfusion rate, operation time and cold isquemia time on the transplant.
Conditional recommendation: The laparoscopic approach could improve the rate of recurrence due to better margins of resection and lower rate of transfusion.
Conditional recommendation: Laparoscopic approach could be beneficial and safe in patients with Child-Pugh grade C.
Recommendation for research: Multicentre studies randomized should be done in the future to obtain firmer conclusions. It would be required studies comparing specific cirrhotic patients according to the Child-Pugh grade. And also on patients with portal vein thrombosis, if in this case the laparoscopic approach could be beneficial.

B.4.b *"Strong" recommendation should be made where there is confidence that, for the vast majority of people, the intervention/action will do more good than harm (or more harm than good). The recommendation should be clearly directive and include 'should/ should not' in the wording.*
"Conditional" recommendations should be made where the intervention/action will do more good than harm (or more harm than good) for most patients, but may include caveats eg on the quality or size of the evidence base, or patient preferences. Conditional recommendations should include 'should be considered/ should not be considered' in the wording.

STRONG/CONDITIONAL

Strong recommendations for the use of laparoscopic approach for hepatic resection in cirrhotic patients should be considered as standard care.
There is insufficient evidence for complex resection in cirrhotic liver and Child-C liver function. That is why conditional evidence is the current status.

5. Recommendations for research

List any aspects of the question that have not been answered and should therefore be highlighted as an area in need of further research.

To date, there are a small number of studies comparing laparoscopic hepatic resection for HCC specifically in patients with cirrhosis. All studies are non-randomized cohorts from single centres; an element of surgeon and selection bias is possible. And the patients in open groups use to be more complex cases, with a localised tumour in posterosuperior segments with a bigger size and needing a major resection. These concerns could affect the potential generalizability of results.
These areas of interest should be considered for research:

- A multicentre case series of laparoscopic resection in cirrhotic HCC patients
- A randomized study with a bigger sample size to avoid selection bias existing in this moment.